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Drugs and Methods for the "Occasional" Anesthetist

RALPH M. WATERS*

UNIVERSITY OF WISCONSIN MEDICAL SCHOOL, MADISON

PREVIOUS to 1900 every graduate of an American medical school was capable of administering the three original inhalational anesthetic agents with reasonable safety. Since 1900 we have learned to use procaine for injection instead of cocaine. We have learned that all anesthetic drugs tend to depress and obstruct respiration. We have learned the means of safeguarding the functions of breathing by careful dosage, by the use of oxygen and artificial airways. Has the necessary equipment for the employment of these safeguards so frightened the modern practitioner of medicine that he no longer has the confidence and competence of his predecessor?

I hope to defend the proposition that the four agents nitrous oxide, ether, chloroform and procaine, with relatively simple apparatus, in the hands of any conscientious and competent physician, can provide safe, pleasant and adequate anesthesia for the majority of the operations in modern surgical practice.

I do not wish to decry in the slightest degree specialization in anesthesia. Nor do I wish to minimize the value of newer drugs and technics which have been added in recent years. Rather is it my desire to emphasize the importance of a thorough medical training for the administrator of anesthetics and simplicity in method of administration, unless or until the status of true specialism is achieved.

In more recent times anesthesia has been influenced by hollow needles, syringes, and rubber tubing. Pharmacologic and pharmaceutical advances have made many new drugs available. Present methods of marketing assure accuracy of dosage of non-volatile agents. All these refinements tempt us to complicate our technics. As a result we are now blessed (and sometimes cursed) with rectal, hypodermic, intravenous, and perineural administration of a great number of drugs, alone and in combination, to produce either local or systemic anesthesia or both simultaneously.

Since all anesthetic agents may and frequently do cause serious depression of the respiratory and other functions, the problems of modern anesthesia grow ever more complicated. To determine the cause and the proper treatment of a condition arising after the simultaneous administration of an opiate and a barbiturate followed by a spinal anesthetic and perhaps further supplemented by the inhalation of nitrous oxide and the injection of some curare-

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like substance is indeed a difficult task. The opiate may have relaxed muscles around the pharynx resulting in respiratory obstruction; the barbiturate may have abolished the carotid mechanism through which lack of oxygen causes a compensatory increase in breathing; the spinal may have paralyzed some of the respiratory muscles; the tension of oxygen in the inspired nitrous oxide may have been too low or the effect of curare may have constricted the lumen of the bronchi.

To determine the cause of trouble in such circumstances may be difficult or impossible for the most experienced specialist. To treat the condition satisfactorily may necessitate a rapid application of technically difficult maneuvers whereby, through a process of elimination of possible causative factors, the guilty one is identified and safe conditions are restored. The terms "premedication" and "basal narcosis" have become very common in our more recent anesthetic vocabulary. We ought to be very sure that such practices are employed to increase the safety and well-being of the patient and not to promote our own convenience or to "cover up" careless or inexpert treatment in the operating room.

You will gather from what I have just said that effects of several different sedative and anesthetic drugs, acting upon one patient simultaneously require a maximum of skill, experience, and knowledge in management if safety is preserved. It is for this reason that I suggest to those who must administer the occasional anesthetic—the student, the intern, the general practitioner, the young surgeon, and the embryo specialist—that each ought to begin by learning about a minimum number of drugs and methods. After mastery of these, he may wisely proceed to more complex efforts. Combinations of drugs and complicated apparatus, and I might add methods temptingly easy of application, do not compensate for lack of basic knowledge, skill and experience. In the hands of the neophyte, they do contribute numerous dangers, embarrassments, and even tragedies.

RALPH M. WATERS

IMPORTANCE OF MEDICAL BACKGROUND AND TRAINING

Had our predecessors realized what a multiplicity of drugs and complexity of technics were to become available in this century, it is difficult to believe that they would have permitted anesthesia to drift outside the practice of medicine in America and become a technical procedure. It was, perhaps, the simplicity of the drugs and methods in common use at the end of the 19th century which caused so large a number to feel that professional respect and economic support for the doctor who administered anesthetics were not justifiable.

The staff and the management of many hospitals of the United States came to look upon anesthesia as a technical matter only. Many of our schools all but ceased to teach anything about anesthesia. The hiatus thus left in the product of our medical education was doubtless a major cause of the former neglect of anesthesia. Neglect rests undisturbed in an atmosphere of ignorance. But a realization of our

former false position has been growing for many years. Ignorance is being dispelled and neglect has now been supplanted by recognition and encouragement.

We now appreciate that a physician who is familiar with the principles and skillful practice of anesthesia can be useful in a rather broad field. His aid is sought in the treatment of pain whatever its cause. Not infrequently his efforts shed some light upon diagnostic problems. In many hospitals, he is consulted regarding the care of acute respiratory and circulatory disorders. Inhalational therapy and even the intravenous administration of fluids are considered a responsibility of the department of anesthesia in some institutions.

However, good teachers and adequate methods of instruction cannot be pulled out of a hat by magic. Our medical schools and larger hospitals are trying, almost frantically in some instances, to establish adequate instruction and service in anesthesia. We have now come to a pretty general realization of the fallacy of the premise that the administration of anesthetic drugs and the supervision of patients affected by them is anything other than the practice of medicine. The demand for physicians who are expert in this branch of our profession, both as teachers and as private practitioners, now far exceeds the supply.

At present the importance of certification of specialists; of long term residencies in all branches of practice, including anesthesia, is being stressed—if not overstressed. Even small hospitals and small communities are demanding that they be furnished with "certified" anesthetists. A sufficient number of these are not now available. It is my belief that, for the vast majority of operations performed in our smaller hospitals, full-time specialists with several years of formal training are not essential. It is also my opinion that after brief instruction and practice in a few technical details, a physician, with his knowledge of modern medicine and all that it implies, is far safer as an anesthetist than is a non-medical person however carefully trained in technical manipulation and use of anesthetics.

The scope of the anesthetist's work interlocks with every phase of modern medical practice. The medical foundation is hard to acquire, not the technical tricks. The three drugs and the simple methods commonly used previous to 1900, and the administration of which was familiar to every doctor, are still available. These together with the rational use of procaine cover our everyday needs.

I suggest that, with interest and attention to the subject, there are in every community an adequate number of physicians who can quickly learn to use these drugs to the satisfaction of everyone. To induce them to do so, they must be encouraged and supported by hospitals and the profession; because it was lack of such encouragement and support which, in former years, almost forced anesthesia out of the practice of medicine.

Every present-day physician is familiar with the physiology of respiration and circulation. It is necessary to re-interpret this knowledge to form a practical concept of various aspects of the transport of oxygen, carbon dioxide, and the anesthetic agents to and from the central nervous system. Intelligent management of all anesthetized patients requires this knowledge so re-interpreted. In addition, there are a few simple technical tricks which can be acquired by experience. A better and quicker way to acquire them is by association and practice with an experienced specialist who is in addition a good teacher.

Every full-time anesthetist ought to be willing to teach the simple fundamentals to other physicians. Often the occasional anesthetists whom he helps may become his junior associates and assistants. Certainly all departments of anesthesia in our large institutions should maintain short periods of instruction aimed to benefit the occasional anesthetist.

The foundation of sane management in anesthesia is the ability to maintain free and adequate breathing and quickly to recognize obstruction and depression of respiration and their secondary effects upon circulation. Early

discovery and correction is important. Here, if ever, "an ounce of prevention is worth a pound of cure." The familiar quotations are apt that "anoxia begets anoxia" and that "anoxia not only stops the machine but wrecks the machinery."

Compressed oxygen is now generally available in operating rooms. The occasional anesthetist will find it to his advantage to become familiar with methods of reducing oxygen to atmospheric pressure and of administering it. The necessary simple mechanical knowledge can be acquired in an hour or two. The early acquisition of skill in the use of artificial airways, both pharyngeal and laryngeal, is of great importance.

The other essential acquisition of the physician who intends to administer an occasional anesthetic is familiarity with one means, for each of a very few drugs, of controlling the dose within safe limits. Mastery of the technic of a simple and complete field block with procaine is essential. Any textbook will explain the common methods. It is well to choose one simple means of using each drug and employ it exclusively until it is mastered, rather than to try several methods and become confused. A few lessons from an experienced teacher who is not "too modern" will be helpful.

Familiarity with the use of oxygen in a simple mask and breathing bag is essential. The dangers and disasters of anesthesia follow interruption of the transport system. Quick establishment of a free airway to the alveoli and artificial respiration if necessary are the remedies. This is true whether the guilty drug be inhaled or injected and regardless of where it is injected.

It seems reasonable therefore that the beginner or the occasional anesthetist will be more ably equipped if he masters the different inhalational methods first.

My associates and I have studied many new agents and methods during the past twenty years. The original three drugs often served as controls for such experiments. Obviously, for fair comparison, administration of the older agents was accompanied by as free breathing, as careful dosage and as much enrichment of respired atmosphere with oxygen as is used with newer drugs.

TABLE 1
INCIDENCE OF ABNORMAL HEPATIC FUNCTION AFTER OPERATION

ANESTHETIC	PER CENT OF CASES
Chloroform	52
Ether	60
Cyclopropane	60
Spinal	66
Pentothal	55
Avertin	33

Comparative statistical evaluation of the clinical results in these cases now convinces us that one, or at most two, of the older agents, administered with equal skill to a particular patient can produce as satisfactory results to surgeon, patient, and anesthetist as are secured by any of the complicated modern methods and combinations. They also require as much skill and effort on our part to produce such satisfactory results.

OPIATES, barbiturates, and tribromethanol (avertin) being respiratory depressants had better be avoided. Saturation with gases or vapors can be much more readily achieved without them. The one non-volatile drug which the occasional anesthetist will find useful is scopolamine in small doses to diminish secretions (or atropin). If non-volatile depressants have not been given, the onset of inadequate breathing during anesthesia can usually be attributed directly to an overdose of vapor, to too great systemic absorption of procaine, or to a lack of oxygen and the appropriate remedy can be applied.

Ethyl chloride, ethylene, cyclopropane, vinyl ether, trichlorethylene, and the newer non-volatile agents vary from the older ones in potency and pharmacologic characteristics. Differences in technical details of their administration tend to confuse the less experienced administrator. They possess no outstanding advantages which skill with nitrous oxide, ether, chloroform, and procaine cannot match. These

drugs, I believe, every doctor ought to be able to administer in a manner acceptable to the patient and the surgeon and with satisfaction to himself. All four are included because they supplement each other. A proper choice of one, or at most two, of the four can be made to serve almost every purpose.

Nitrous oxide, when inhaled for several minutes in concentrations below 60 per cent, abolishes the sensation of pain without producing unconsciousness. Analgesia produced in this manner has a wider application than is generally appreciated. When nitrous oxide is diluted with less than 40 per cent oxygen, and inhaled over a period of several minutes, unconsciousness results, but muscle-tone and reflex activity are not abolished. If used with as much oxygen as normal atmosphere contains and when ample time is allowed for saturation of the blood and tissues, nitrous oxide serves admirably to abolish the pain of brief operations or of those which do not require relaxation of muscles or the absence of reflex activity.

TABLE 2

65 CASES—CHLOROFORM

		AVERAGE
Time	=	120 minutes (45—240)
Total	=	39 cc. (12—103)
Inh.	=	0.55 Vol. per cent (0.23—0.96)
Bl.	=	6.2 mgm. per cent (2.2—12.0)
$Bl.O_2$	=	16.2 Vol. per cent (10.3—21)
$Bl.CO_2$	=	46 Vol. per cent (39—59.5)

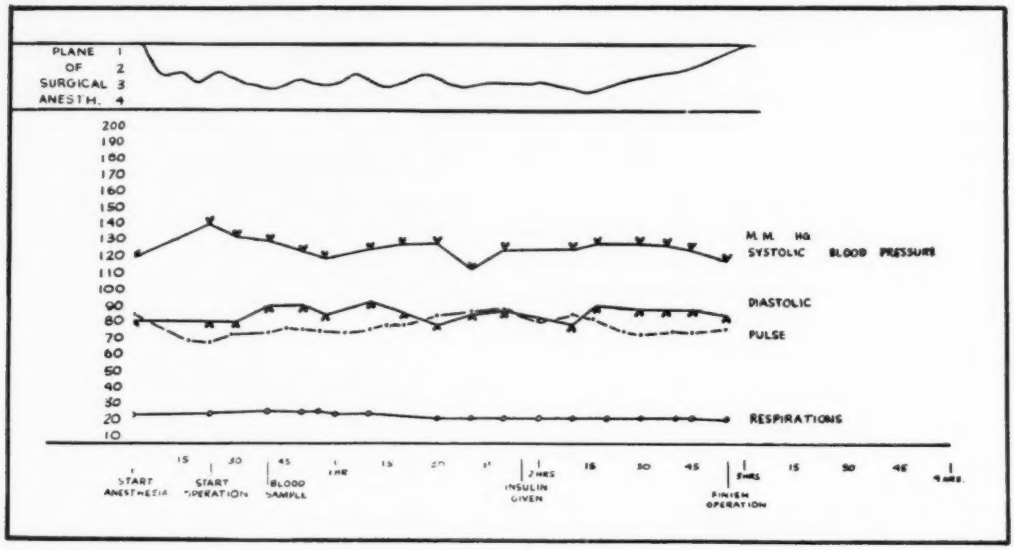
In my estimation, the dangers of nitrous oxide have been greatly exaggerated in recent years. They have certainly been enhanced by the injudicious use of depressant drugs as adjuvants. Nitrous oxide is also convenient for the production of rapid and pleasant unconsciousness preceding and during the induction of ether anesthesia. Experience and skill in making the transition and in permitting the proper accumulation of expired carbon dioxide during such an induction adds to the speed and smoothness of the procedure.

Ether, skillfully administered, can be made to produce satisfactory anesthesia for nearly all operations during which a source of ignition is not present. Added oxygen, or nitrous oxide mixed with oxygen, enhances the hazard of fire and explosion if a flame, spark, or static charge is anticipated. Slow and gradual changes in the concentration of vapor prevent many of the more common complications. Mucous secretion, struggling, and obstructed respiration during induction can thus be minimized. Failure to saturate with adequate vapor-tension before operation is begun is the usual fault in the administration of ether.

AN INADVERTENT overdose during induction, causing arrest of respiration, rarely needs treatment other than brief interruption of administration. Respiratory arrest during either nitrous oxide or ether anesthesia is rarely serious unless there is simultaneous scarcity of oxygen in the patient's tissues. Confidence that the lungs can be inflated with air or preferably oxygen is the only safeguard necessary. A minimum flow of oxygen under the mask, even with "open drop" technic, is essential to prevent hypoxia.

Chloroform is added to this list of simple drugs for the occasional anesthetist after careful consideration. Obviously on certain occasions, he must be in possession of a completely potent and universally applicable agent which can be used without hazard of fire. The technical dangers with chloroform are great. It seems to me however that they are no greater for the occasional anesthetist than are other means of avoiding the danger of explosions. The administration of tribromethanol by rectum, intravenous administration of a derivative of barbituric acid or blocking of the nerve supply to the region of operation are accompanied by dangers, too. Admittedly, individual skills and the feeling of confidence which goes with them are important. If your confidence lies with one of the methods just mentioned, well and good. However, even in the hands of the relatively inexperienced it is my belief that chloroform can serve adequately and safely.

In the absence of nitrous oxide, chloroform affords a means, agreeable to the patient and



Gastric Resection (Ulcer) January 11, 1947. Male: Age 59; Weight 220 lbs.; 9.6 gm. Hb. Controlled Diabetes. Septic arthritis of hip. Questionable old cardiac infarct. Physical status: poor. Premedication: Morph. Sulph. 1/16 grain & scopolamine 1/200 grain. Chloroform—open drop. (No added oxygen.)

convenient to the anesthetist, of inducing unconsciousness for a brief operation or for the induction preceding ether. Safeguards during the administration of chloroform are, first, patience and deliberation in increasing the vapor-tension; second, constant palpation of the patient's pulse, and third, addition of oxygen to the respired atmosphere.

Maintenance of the freest of free breathing is very desirable. Rapid increase in the concentrations inhaled or a sudden high tension entering the alveoli, due to a deep breath or other cause, may allow a marked increase in tension of chloroform in the blood to reach the heart suddenly. Such injudicious overdose may cause myocardial depression or even cardiac arrest. Ventricular fibrillation, so often mentioned in the literature, is extremely rare in man.

PROMPT artificial ventilation of the lungs, quickly to reduce the alveolar concentration, is the remedy for overdose of chloroform. Constant palpation of the pulse is important. If one remembers that some thirty seconds intervene between the dropping of liquid chloroform on a mask and the contact of the corresponding vapor-tension with the muscles of the heart, deliberation seems justified. If a sudden change in the pulse is palpated or if respiration is markedly depressed or arrested, interruption of administration and quick ventilation of the lungs with oxygen will restore the heart at once.

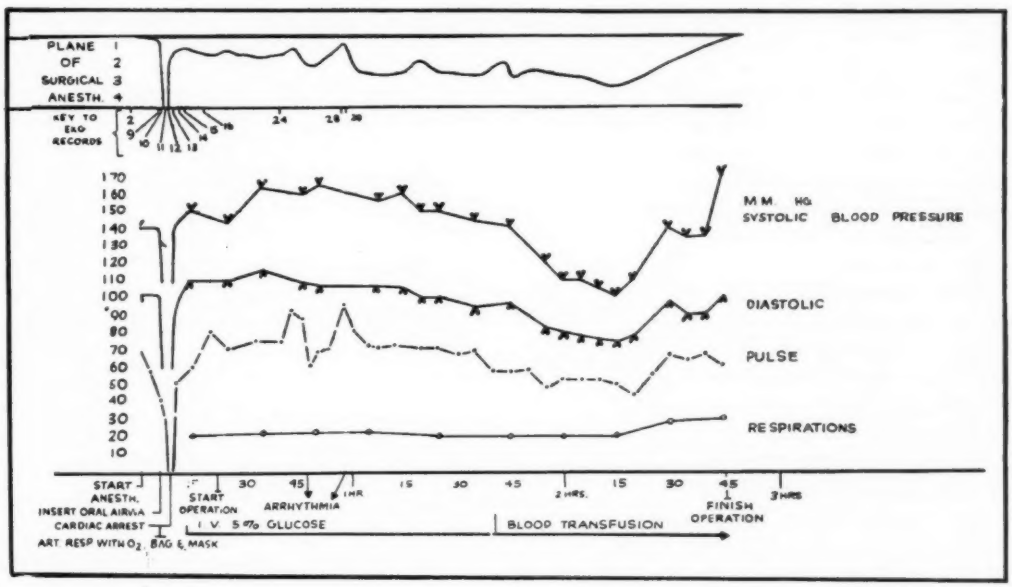
Evidence of acute cardiac depression has been observed 12 times by my associates and me at the Wisconsin General Hospital during 1,000 administrations of chloroform. In every instance a relatively sudden and large increase in concentration preceded the depression. On one of these occasions the heart is known to have stopped beating. Prompt inflation of the lungs with oxygen almost instantly restored what appeared to be normal conditions in every instance. What may appear to be almost infinitesimal amounts of chloroform added to nitrous

oxide and oxygen serve materially to extend the field of usefulness of that agent. Vaporized with oxygen, it may be made to produce prolonged analgesia, or very light anesthesia, if the necessarily minimal strength of vapor can be maintained.

Procaine is well established as a local anesthetic. Its dangers and disadvantages are more thoroughly understood than those of any other agent. Procaine, therefore, is recommended as the occasional anesthetist's local agent. A minor operation can often be performed more safely with procaine upon a patient whose stomach is not empty or who must be ambulatory when the operation is finished.

Spinal administration—If this method is attempted by the beginner, procaine is probably the safest drug. Failure with a locally acting drug, including spinal, creates a temptation to supplement with inhalational methods. A real hazard is thus created. Not only is the mental state of the patient inappropriate for tranquil induction but also the same condition which led to the original choice may make unconsciousness dangerous. Marked and sudden circulatory depression, both central and peripheral may occur during spinal anesthesia. Respiratory paralysis, partial or complete, is not infrequent. Artificial respiration applied promptly is the first remedy. Hence the importance of a knowledge of inhalational technics and oxygen before other technics are attempted.

Spinal administrations tempt the inexperienced because they are so easy. This very simplicity, however, as with the intravenous and other administration of non-volatile drugs, may be a source of danger. Anyone can inject through a hollow needle. Knowledge and ex-



Gastric Resection (Carcinoma) March 25, 1947. Male: Age 73; Weight 116 lbs.; 10.5 gm. Hb. Coronary sclerosis, impaired kidney function. Physical status: poor. Premedication: Scopolamine 1/200 grain. Chloroform—open drop (50 cc.) with oxygen added under mask.

perience are nevertheless necessary to foresee the physiologic and pharmacologic changes that may result in a patient following such injections. Prompt action, with technically difficult maneuvers, may be necessary at times to restore normal conditions. The beginner must decide for himself the direction of his greatest skill and knowledge. He must aim at maximum safety for his patient with due consideration for the convenience of the surgeon for whom he works.

SUMMARY

It is strange, but nevertheless quite true, that the three anesthetic agents which first came into general use are still quite adequate for our everyday needs. Local anesthesia is the one outstanding addition in the past fifty years. By this I do not mean to imply that no other advances in anesthesia have been made. Rather do I wish to emphasize that, when nitrous oxide, ether, or chloroform is used with a comparable degree of modern technical skill and intelligence the results are not inferior to those secured by the use of more recently popularized drugs and methods.

I believe the present scarcity of anesthetists can almost be declared to be an emergency. To meet this acute need, I have suggested that we ought to encourage what may be called the occasional, part-time, or general practitioner anesthetist. Pursuant to that aim, the following things seem desirable.

1. We, the medical profession, ought to reassume the responsibility regarding anesthesia which our forbears of the 19th century held and which we all but lost in the early years of this century.

2. Hospital management and the profession in general ought to encourage physicians to perfect themselves in modern methods of treating and preventing pain. Such encouragement must include both economic and professional recognition and respect. Whether such persons devote all or only a part of their time to anesthesia is immaterial. The general practitioner's diagnosis can, in a majority of cases, be quite as thorough as that of the full-time consultant in internal medicine. Similarly, the occasional or part-time anesthetist can render a service to his community which is satisfying to himself, to his fellow practitioners, and his patients.

3. Acquisition of skill through practice in administering nitrous oxide, ether, and chloroform with modern technics (free and adequate breathing, careful dosage, and the addition of oxygen) promises more for the occasional anesthetist (or for the specialist in his early training period) than does an attempt to use every new agent suggested. To get the best results from these three agents or from a simple field-block with procaine, requires the ultimate in skill of administration and management. Mastery in the use of these, I believe, should be the goal of the beginner.

4. It should be the duty of those of us who teach to see that a thorough groundwork of fundamental knowledge, and skill with the four primary agents precedes instruction in modern frills. Help for the undergraduate, for the intern, and the prospective occasional anesthetist is an integral part of our duty.

5. The aim of anesthesia is the welfare of the patient. The drugs and methods used should be within the capabilities of the anesthetist who is available. His efforts must result in a patient upon whom the surgeon can work with ease and confidence. It is my conclusion that, under the circumstances which confront us at present, the occasional anesthetist can contribute materially in bringing the maximum benefits of surgery to all of our patients.

Resection and Primary Anastomosis for Lesions of the Left Portion of the Colon

JOHN M. WAUGH[1] and MONFORD D. CUSTER, JR.[2]

ROCHESTER, MINNESOTA

In DECEMBER 1945 we published an account[1] of the technic and the results of the first 50 primary resections of the left portion of the colon performed by one of the authors (Waugh). Continuity was restored in all cases by immediate aseptic end-to-end anastomosis without complemental proximal colostomy. There were 2 deaths in this series, resulting in a mortality rate of 4 per cent. The mean hospitalization period for the surviving 48 patients was 21.4 days.

The literature subsequent to the time of submission of this earlier report for publication has contained numerous excellent articles pertaining to this subject. With the notable exceptions of Lahey,[2] Maingot,[3] and Lloyd-Davies,[4] the majority of recent opinion frankly favors one-stage resection as opposed to the multiple-stage exteriorization type of procedure. Babcock and Bacon[5] have expressed a preference for the former method because it is more radical as well as more generally satisfactory, and have stated they have discarded the Mikulicz-Paul technic except to terminate an operation quickly in the face of gross contamination. Wangensteen[6] reported a combined series of 139 primary resections performed without simultaneous colostomy with a mortality rate of 5 per cent. In a similar series of 20 cases reported by Meyer, Sheridan, and Kozoll[7] from the Cook County Hospital, the mortality rate was also 5 per cent, the one death resulting from pulmonary embolism. The mortality rate in McMillan's[8] series of 27 cases was 3.7 per cent, and in that of Clute and Kenney[9], 6 per cent for 48 cases.

White and Amendola[10] reviewed the history of resection of the colon at the Roosevelt Hospital in New York City, where exteriorization has been abandoned in recent years in favor of primary resection. In support of the latter procedure, these authors regarded it as safer than extraperitoneal resection in addition to offering the advantages of one operation, a shorter stay in a hospital, and increased resectability rate. They, however, advocated protection of the anastomosis by means of proximal colostomy or cecostomy, as did also Coller and Vaughan.[11] The latter authors, in discussing the problem of selection of operation, stressed the striking reduction in length of hospitalization accomplished by means of immediate anastomosis.

The British surgeons, Maingot[3] and Lloyd-Davies,[4] on the other hand, both strongly advocated the Mikulicz-Paul resection on the

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Read at the meeting of the Interstate Postgraduate Medical Association of North America, St. Louis, Missouri, October 14 to 17, 1947.

ground of increased safety. In Lloyd-Davies' series of 73 exteriorization procedures there were 3 deaths, resulting in a mortality rate of 4.1 per cent. In this country Lahey[2] remains the chief proponent of a staged procedure for both sides of the colon. However, he has no quarrel whatsoever with primary resection and has stated that his personal preference for the Mikulicz operation is dependent in a measure on his wide experience with it in the past. Other advantages which Lahey has emphasized are the additional safety provided by immediate decompression and the ability to examine the remaining loops of bowel with an endoscope for adjacent polyps. His operability rate for the procedure is 83 per cent and the mortality rate is 2.7 per cent, the latter figure being one which most certainly approaches an irreducible minimum for this type of surgery.

Although a difference of opinion still exists, the trend appears to favor the single-stage operation very strongly. That this approach is a sound one, surgically speaking, is borne out by the fact that substantial series of cases are now being reported in which the risk of the operation is in the neighborhood of 5 per cent. This remarkable reduction in mortality has been attributed by most surgeons to the advent of chemotherapy, although Wangensteen[6] does not rely on the routine use of sulfonamide compounds either orally (sulfasuxidine, sulfathaladine), intraperitoneally, or parenterally.

From the pathologic standpoint additional support has been gained for segmental resection (anterior resection) of lesions so distally located within the lower portion of the sigmoid, the rectosigmoid, and the upper portion of the rectum as to preclude exteriorization. These lesions have heretofore required abdominoperineal resection, which procedure necessitates permanent sacrifice of the normal sphincter mechanism. The recent work of Glover and of one of the authors (Waugh)[12] in respect to the retrograde lymphatic spread of rectosigmoidal and rectal malignant lesions has convinced us that anterior resection of these lesions is as thoroughly curative as the more extensive Miles type of resection.

JOHN M. WAUGH

THE present report is concerned with 147 new cases. Thus the total number of cases, including the 50 previously reported, is 197, all of which operations were performed during the five-year period from January 1942 to December 1946, inclusive.

GROUPING OF CASES

In our original report we found it convenient to divide our cases into two groups in accordance with the location of the lesion in the bowel. This arrangement is again followed, since we have found a relatively constant statistical difference between these groups in regard to mortality, length of convalescence, and incidence of complications.

Group A (78 cases) comprises those lesions situated between the midtransverse and the midsigmoid colon, inclusive, for which an exteriorization procedure would otherwise have been performed. Group B (69 cases) comprises

those lesions situated in the lower part of the sigmoid, the rectosigmoid, and the upper part of the rectum for which combined abdominoperineal resection would otherwise have been performed. Figure 1 represents the distribution of these lesions.

MONFORD D. CUSTER, JR.

TYPE OF PATHOLOGIC CHANGE

The types of pathologic change encountered were carcinoma of the colon, 131; sigmoidal diverticulitis, 10; tubo-ovarian abscess with involvement of sigmoid, 2; primary carcinoma of the jejunum with involvement of the transverse colon, 1; islet cell carcinoma of the pancreas necessitating removal of the distal portion of the transverse colon, 1; benign stricture, 1; inflammatory ulcer, 1.

In addition to a segmental resection of the colon in each case, the following additional resections were performed: left fallopian tube, 9; left ovary, 9; segment of jejunum, 2; segment of urinary bladder, 2; uterus, 3; leiomyoma of uterus, 2; tail of pancreas, 2; spleen, 1. Thus a total of 30 additional organs were resected in whole or part.

RESECTABILITY RATE

The resectability rate for cases in which exploration was performed for malignant lesions of the left portion of the colon situated far enough proximally to be amenable to either segmental resection and anastomosis or to extraperitoneal resection was 81.3 per cent (Table 1). This figure was derived as follows: A total of 278 malignant lesions of this type were explored during the five-year period 1942 to 1946, inclusive. Of these, 226 were resected, 176 by segmental resection with immediate end-to-end anastomosis, and an additional 50 by extraperitoneal resection. A staged procedure was elected in the latter group in nearly all instances because of inability to prepare the bowel properly owing to an obstructing lesion which was chronic in nature. The remaining 52 lesions were considered inoperable by virtue of extensive invasion of surrounding structures with or without hepatic metastasis. In 47 of these 52 inoperable cases, palliative colostomy operations were performed.

MORTALITY RATE

Nine of the 147 patients failed to survive the operation, giving a hospital mortality rate of 6.1 per cent. Considering the combined series of 197 cases, which includes the 50 previously reported, there were 11 deaths, giving an overall mortality rate of 5.6 per cent.

The mortality rates for group A and group B in the present series are 5.1 per cent and 7.2 per cent, respectively. The increased risk associated with resection of the lower-lying lesions is felt to be related to the technical difficulty of effecting a perfect anastomosis, with resulting failure of primary healing which occurs occasionally in such operations. Table 2 summarizes the mortality statistics.

Table 3 lists the causes of the 9 deaths. It will be noted that 5 patients died of causes (peri-

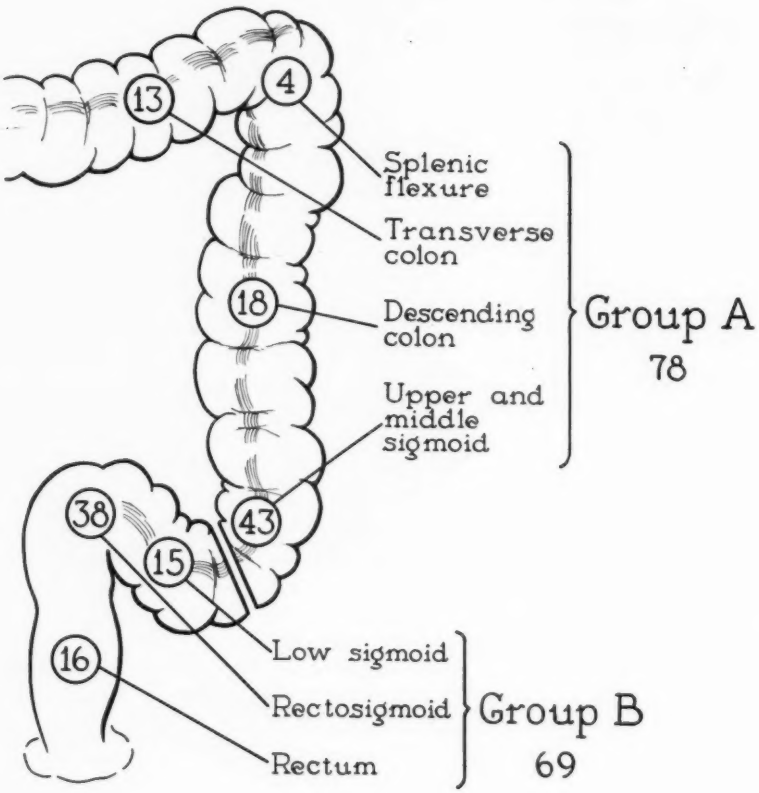

Figure 1. Site of lesions and number of cases in which lesions were at various sites in groups A and B.

tonitis or hemorrhage or both) attributable to the operation. The remaining 4 patients died of unrelated accidents. All of the latter group had postmortem examination, except the one presumably dying of renal failure.

RESECTIONS FOR MALIGNANT LESIONS

In Table 4 it is of interest to compare the hospital mortality rates of curative operations and palliative operations. The mortality rate for curative resections was less than 5 per cent, whereas the palliative resections involved a mortality rate of 20 per cent. The risk of resection of a malignant lesion was found to be slightly less than that of a benign lesion.

COLOSTOMY

We remain convinced of the fact that for resection of lesions in group A, when the bowels are unobstructed and adequately prepared, proximal colostomy is an unnecessary adjunct to the procedure. We also feel that adequate decompression is assured in the majority of resections of group B lesions by means of a 38°F. rectal tube which is passed during the operation through the anus to a point well beyond the anastomosis. However, in group B cases in which the anastomosis appears to be imperfect after its completion, it is our practice to protect the suture line further by means of a temporary complemental loop colonic stoma situated proximally. Complemental colostomy of this type

TABLE 1

RESECTABILITY RATE FOR MALIGNANT LESIONS OF LEFT PORTION OF COLON* FOR FIVE-YEAR PERIOD 1942-1946, INCLUSIVE

Operable		
Segmental resection with primary anastomosis	176	
Extraperitoneal resection	50	
Total resection		226
Inoperable		
Exploration without colostomy or resection	5	
Palliative colostomy without resection	47	
Total inoperable lesions		52
Total malignant lesions explored		278
Resectability rate for 278 consecutive cases		81.3%

*Exclusive of those treated by combined abdominoperineal resection.

TABLE 2

MORTALITY RATE

	Cases	Deaths	Mortality Rate, Per Cent
Group A (new cases)	78	4	5.1
Group B (new cases)	69	5	7.2
Combined new cases	147	9	6.1
Previously reported	50	2	4.0
All cases (new and previously reported)	197	11	5.6

TABLE

CAUSE OF DEATH

	Cases
Peritonitis	4
Hemorrhage	1
Renal failure, anuria	1
Cardiac failure	1
Cerebrovascular accident	1
Unexplained	1
Total	9

was utilized in 8 of the 67 resections in group B.

IT IS interesting to note that simultaneously established colonic stomas were present and functioning in 3 of 6 cases in which death resulted from causes related directly to the operation. In the fourth case, death resulted from peritonitis secondary to perforation of the ileum at the site of a Witzel enterostomy that had been established after evisceration, which occurred ten days after the original operation. In the fifth case, necropsy was not permitted so that the exact condition of the anastomosis and the adjacent portion of the bowel is unknown. In only one instance did a patient without colonic stoma die of peritonitis and this patient, interestingly enough, was demonstrated at necropsy to have a concomitant bronchogenic carcinoma. Thus it is questionable in our minds whether even routine simultaneous decompression by means of colostomy would have favorably affected the mortality rate in this series (group B).

The 10 colostomies in group A were all previously performed for the following reasons: emergency decompression, 4; sigmoidovesical or sigmoidocutaneous fistula, 3; acute diverticulitis, 1; inadequate preparation of bowel at time of initial exploration, 2.

Of the 14 colonic stomas in group B, 8 were established as protective vents at the time of operation as described previously. One was established on the eighth postoperative day because of the development of a rectovaginal fistula and one for a sigmoidocutaneous fistula as a preliminary procedure. The remaining 4 had been previously established as emergency measures for acute obstruction.

PALLIATION

We are in accord with Babcock and Bacon,[5] who strongly advocate palliative resection. It is our feeling that obviation of the inevitable colostomy greatly outweighs the added risk from the viewpoint of both the patient and his family. In this series, 10 resections were frankly palliative either because of hepatic metastasis or because of nodal involvement beyond the limits of resectability. Two of these patients failed to survive the operation.

COMPLICATIONS

Group A—Of the 76 survivors in this group, one had a serious complication. This patient had multiple enterocutaneous fistulas requiring re-exploration eleven months after resection. The fistulas were found to arise from a loop of ileum which had become incarcerated in a

TABLE 4
RESECTIONS

Group	Cases	Deaths	Mortality Rate, Per Cent
Malignant lesions			
Group A curative...	59	3	5.1
Group B curative....	63	3	4.8
Total curative	122	6	4.9
Group A palliative...	6	0	0
Group B palliative...	4	2	50.0
Total palliative ...	10	2	20.0
Total cases	132	8	6.1
Benign lesions			
Total cases	15	1	6.7

small incisional hernia. The colocolonic anastomosis was completely healed. Convalescence from this operation was uneventful.

Other complications in group A included cystitis, 3; thrombophlebitis, 2; wound infection, 1; hematoma in wound, 1; obstruction of the vesical neck, 1; drug reaction (sulfadiazine), 1.

Group B—There was a considerably higher relative incidence of complications together with a course of convalescence which was in general less smooth and more prolonged than that of the patients in group A. This is in accord both with our previous findings and with the experience of Wangensteen.[6] The latter noted delayed healing following resection of low-lying lesions, and attributed it to vascular impairment associated with the extensive mobilization which is required from the anterior sacral space.

THREE of the 52 survivors in group B had serious complications related directly to the resection of the bowel.

1. One patient had a large abscess in the hollow of the sacrum with prolonged drainage, necessitating hospitalization for ninety-four days. This complication developed despite a well-functioning colonic stoma established at the time of resection. However, the symptoms gradually subsided with conservative treatment, and it was possible to close the stoma successfully eighteen months after the initial operation was done.

2. One patient had a rectovaginal fistula eight days after resection of a carcinoma of the rectum. Digital examination revealed the anastomosis to have partially separated. A descending loop colostomy was performed. The fistula healed spontaneously and the stoma was closed eight months later.

3. One patient had a large pelvic abscess, severe hemorrhage, and eventual separation of the anastomosis after sigmoidal resection for diverticulitis in August 1944. After a prolonged septic course, the bowel was re-anastomosed in February 1946. Convalescence was uneventful and it was possible to close the proximal stoma two months later.

Other complications occurring in group B included cystitis, 5; wound infection, 5; pelvic cellulitis, 4; transient fecal fistula closing spontaneously, 4; urinary retention (transient), 3; partial disruption of suture line healing spontaneously, 2; pulmonary embolus, 2; temporary (six months) diarrhea improving spontaneously, 2; thrombophlebitis, 2; hemorrhage, 1; parotitis, 1; transient ascites, 1; transient obstruction of the small bowel spontaneously relieved, 1.

TABLE 5
HOSPITALIZATION TIME

Group	Without Colostomy		With Colostomy	
	Cases	Ave. No. of Days	Cases	Ave. No. of Days
Group A	64	16.5	10	54.5
Group B	50	22.7	14	60.0
Total	114	19.0	24	57.4

HOSPITALIZATION

Table 5 contains figures relative to convalescence in the hospital. It will be noted that the average period of hospitalization for all surviving patients without colostomy is nineteen days. This compares favorably with the prolonged convalescence associated with either extraperitoneal or abdominoperineal resection.

It should also be noted that a longer period of hospitalization may be expected in group B

than in group A patients in accord with the known higher incidence of complications.

SUMMARY AND CONCLUSIONS

Primary aseptic anastomosis was performed in 197 consecutive cases (50 previously reported and 147 additional cases) after resection of lesions of the left portion of the colon. Eleven patients died, resulting in a mortality rate of 5.6 per cent.

For lesions of the middle part of the sigmoid and above, this operation provides a safe, curative one-stage procedure, with the hospital convalescence seldom exceeding three weeks. For lesions of the lower part of the sigmoid, the rectosigmoid, and the upper half of the rectum, this technic provides for the eradication of malignant lesions with preservation of the lower part of the rectum and the sphincter ani. The average period of convalescence in the hospital from this operation (anterior resection) is approximately one month.

The following conclusions are drawn:

1. Primary anastomosis is the procedure of choice after resection of lesions in the nonobstructed, prepared bowel.

2. Proximal colostomy is unnecessary for lesions of the middle part of the sigmoid or above, and is of questionable necessity or value for more distally situated lesions.

3. Palliative resection with immediate restoration of intestinal continuity is a logical and kindly approach despite an increase of risk.

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TOXICITY OF CHEMOTHERAPEUTIC AGENTS

In a study of antibiotics and sulfonamides, Perrin Long describes the various toxic reactions of chemotherapeutic agents. Of four sulfonamides investigated, sulfadiazine is by far the least toxic, with sulfanilamide next. Sulfathiazole is the most toxic of the four drugs tested. In similar studies of antibiotics, penicillin was found to be much less toxic than streptomycin; but the toxicity of penicillin is sufficient to demand caution in its use.

Long speaks against the local use of sulfonamides and the antibiotics. He believes that the external use of these agents as dusting powders, creams, lotions, and salves is generally contraindicated, for by so using them in minor infections the patient runs the risk of becoming sensitized to a drug which later might save his life.

Newer Drugs in the Treatment of Allergic Diseases

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The average physician is frequently confused by the large array of drugs introduced in the last decade for treating allergic disease. And then if to all these drugs are added those still in use from an earlier period, his confusion increases. Some of these remedies are valuable, many are worthless, while others have limited value. Unjust advertising claims and uncritical medical articles add further to this bewilderment. These reasons prompt the presentation of an evaluation of some of these drugs.

SYMPATHOMIMETIC OR VASOCONSTRICTING DRUGS

Epinephrine is still a very useful drug in the temporary relief of allergic manifestations. In addition to the customary use of hypodermic injections of epinephrine 1:1000, inhalations of epinephrine solution of 1:100 are now commonly employed for self-medication in asthma. Several manufacturers have marketed stronger solutions and have sold them under trade names directly to the patient.

Inhalations of epinephrine are useful in moderate attacks of asthma and have the advantage of being relatively free from systemic effects and of permitting the patient to use effective medication early in the attack. However, if used to excess or indiscriminately such medication may do considerable harm. It is therefore essential that it be employed only under direction of the physician.

Another epinephrine product introduced in recent years is a slowly absorbing, injectable preparation intended to prolong the duration of action of the drug. My experience indicates that such preparations do not produce the desired effect consistently; sometimes they are too slow to do any good, while at other times they are so rapid that the large dose of the drug produces violent reactions. This clinical experience has been amplified by pharmacologic experiments on animals.

Various modifications of ephedrine and drugs having ephedrine-like action have been introduced in recent years for oral use. Racephedrine (d-l-ephedrine) is somewhat less potent and less toxic than natural ephedrine, and may be used often as a substitute when the latter is not tolerated. Propadrine hydrochloride (diphenyl-l-amino-2-propanol-1-hydrochloride), in doses of ⅜ to ¾ gr. (25 to 50 mg.), is a useful drug for those who obtain too much excitation

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from ephedrine; however, it is not as constantly effective as ephedrine.

Many commercial ephedrine products differ only in the nature of the sedative added to counteract the stimulating effect of ephedrine. The combination of choice should depend on the degree and duration of the sedation desired, the individual patient's behavior, and some other circumstances.

For topical use as nasal vasoconstrictors, a number of medicaments have been added to the old list of ephedrine products. A very popular form is the benzedrine inhaler. If not used too frequently it is a valuable vasoconstrictor in many instances. Tuamine solutions and inhalers have been marketed in recent years. Among the topical vasoconstrictors which are milder than ephedrine are paredrine hydrobromide, 1 per cent, propadrine hydrochloride, 1 to 3 per cent, and racephedrine hydrochloride, 1 per cent. Two products in particular are more potent than ephedrine: Neosynephrine hydrochloride is usually employed in ¼ per cent strength and occasionally in 1 per cent concentration in obstinate cases. Privine hydrochloride is the most potent of all and is marketed in strengths of 1/20 per cent (0.05 per cent) and 1/10 per cent (0.1 per cent).

The disadvantage of very potent vasoconstrictors is that the local ischemia they produce may be so complete that when the effect wears off there results a compensatory vasodilatation. This "rebound" congestion calls for further use of vasoconstrictors. Thus a vicious cycle may result in which the congestion is maintained because of the use of drops. Our experience has made us loath to employ any strong topical remedies in allergic patients, unless intended only for occasional use. Recently I have found that satisfactory shrinking effects could be obtained with Privine solutions of 0.03 per cent or 0.02 per cent, with much less of rebound penalty.

SAMUEL M. FEINBERG

THERE is an increasing tendency for addition of antiseptics, sulfonamides or antibiotic drugs to vasoconstrictors. The average allergic nose neither needs nor tolerates antiseptics well. The promiscuous use of penicillin, sulfonamides, and similar drugs in conditions where they are not needed may eventuate into an induced sensitivity which could interfere with the use of such drug when the need is desperate.

ANTIBIOTIC THERAPY

Since bronchial infection is an accepted cause of a large group of asthma cases it is natural the modern bacteriocidal substances should be tried for them. Several workers have claimed varying degrees of success with sulfonamides. Applebaum employed sulfathiazole aerosols and claimed improvement in 86 per cent of the patients treated.

Schonwald and Deppe were the first to report on the use of penicillin in a large series of asthma cases. They gave injections of rather small doses and claimed excellent results. The results of Hampton and his associates as well as those of Leopold and Cooke were moder-

ately favorable. Barach and his co-workers obtained encouraging results by using penicillin aerosols; Vermilye gave an enthusiastic account of efficacy of penicillin aerosols in asthma.

My experience is that penicillin aerosol therapy is helpful in some cases of infectious asthma. It is, of course, of no help in the ordinary allergic case. Since there are many patients with asthma whose allergic causes cannot be identified and which are nevertheless neither intrinsic nor bacterial, it stands to reason that a large proportion of this group will not respond to penicillin. Although more lasting results may be obtained in some cases of infectious asthma, in most instances the effects of penicillin treatment are apt to be temporary. The more chronic and more complicated the asthma the less likely is it apt to be influenced materially by penicillin. When special apparatus for the administration of penicillin aerosols is not practicable the patient may use an ordinary hand nebulizer, aerosolizing about one-half cc. of a solution containing 20,000 units of the drug, every three hours.

Although allergic reactions to penicillin are quite common there is no evidence that the asthmatic group is more prone to such reactions. It is possible that streptomycin therapy may be helpful either alone or combined with penicillin in certain types of asthma. Allergic reactions to streptomycin must also be considered, since Keefer and his associates have reported an incidence of about 5 per cent of skin rashes following streptomycin administration.

VITAMINS

Practically all known vitamins have had their advocates in the treatment of allergic disease. The favorable claims for vitamin D, particularly with large doses (60,000 to 300,000 I.U.), have not been substantiated. Vitamin A has been of no help, either alone or added to D. Thiamin has not been effective and the claims for lactoflavin have not been corroborated. Nicotinic acid and nicotinamide offer no benefit, although the vasodilating effects of nicotinic acid, particularly parenterally, may have at times a desirable but temporary pharmacologic effect.

Vitamin E was found to be of no value in allergy. The claims for inhibition of anaphylaxis and sensitization to chemicals by vitamin P have not been confirmed. The good results reported with vitamin K in urticaria by one worker have not been possible to duplicate in my practice nor in that of my colleagues.

Vitamin C has probably been the most frequently used vitamin in allergy. The claims of Hagiesco and his associates for the effectiveness of intravenous injections of vitamin C in asthma were negated by subsequent workers. The enthusiastic report of Holmes and Alexander in 1942 was largely responsible for the widespread use of ascorbic acid in hay fever and other allergic conditions. Hebald and Engelsher reported that their results with this vitamin were poor. Friedlaender and I showed that hay fever subjects had a normal blood level of vitamin C and that large doses of the vitamin produced the usual saturation blood levels but had no effect on the course of the hay fever or asthma. In spite of these reports and others and the almost unanimous opinion of allergists that vitamin C is of no benefit in allergic conditions, it still continues to be a form of self-medication by many hay fever sufferers.

HORMONES

Endocrine disturbances are no more common in allergic people than in the general population, and when they are present they are usually neither the causes nor the results of the allergy. Of course, any profound metabolic alteration may aggravate an existing allergy. Thus, a hyperthyroidism may upset the nervous system sufficiently to make an asthma worse. Hypothyroidism rarely has the same effect. If hypothyroidism exists thyroid medication is indicated, but rarely will it result in improvement of the allergy. Parathyroid, spleen or liver extracts, advocated at one time or another as remedies for allergic disease, may be regarded as devoid of any particular merit, except for the slight nonspecific effects that may occur from their injection.

Cortical extract of the suprarenal gland, at first advocated in the treatment of allergic disease, has been finally judged lacking in effectiveness. Desoxycorticosterone has not been helpful, and the claims for the efficacy of oral administration of a concentrate of the entire suprarenal gland have not been confirmed.

It is common experience that allergic manifestations are apt to be influenced by the cyclic changes in the physiology of sex hormones. The frequent aggravation of allergic symptoms in the premenstrual phase, the improvement in allergic manifestations often occurring during pregnancy, and the changes in allergic status in one direction or another sometimes occurring at puberty or menopause, are accepted phenomena.

Several explanations for these observations have been offered. Some are of the opinion that these manifestations may represent an allergy to a hormone. Others believe that hormones may play a specific role in the production of allergy. The most likely explanation, however, is that endocrine disturbances, like other secondary causes, may act in a nonspecific manner by upsetting the allergic equilibrium. Theelin and other sex hormones have had very little effect in such cases. On the basis of Zondek's claims I have been able to suspect at times an autogenous allergy to estrogenic hormones and have been successful in a few instances in relieving allergic symptoms by giving desensitizing injections of the hormone.

MINERALS AND ACIDS

Since there is no calcium deficiency in allergy and since large doses of calcium salts orally do not modify capillary permeability, there is very little indication for the use of calcium in allergic patients. Occasionally urticarial lesions are benefited temporarily by intravenous injections of calcium salts. Potassium chloride still continues to be sold over the counter and is warmly recommended by some medical columnists, although the evidence is conclusive that it is of almost no value in allergy.

Phosphorus compounds had a temporary vogue because of an alleged phosphorus deficiency in allergy: this deficiency was subsequently disproved by carefully conducted laboratory tests. Hydrochloric and nitrohydrochloric acids have had their day as specific remedies for hay fever; it is now generally conceded that acids are only of occasional help in food allergy insofar as they might at times improve digestion.

Arsenic, an old remedy for asthma mentioned in text books of the nineteenth century, has recently had a revival of interest. Arsenic helps only a small percentage of the sufferers, although it not infrequently aids the general condition by improving appetite and perhaps other functions. It must be remembered, however, that long continued and unsupervised arsenic medication may produce serious toxic effects.

MISCELLANEOUS REMEDIES

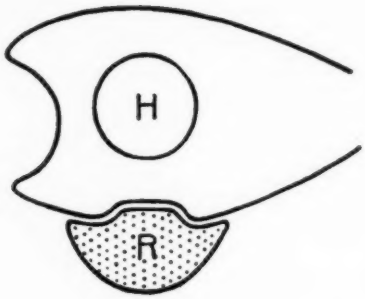
Anoxemia is not present in the usual asthma attack and oxygen is therefore not ordinarily indicated. In status asthmaticus or in a very acute asthma attack with cyanosis oxygen may be helpful. The use of inhalation mixtures of 80 per cent helium and 20 per cent oxygen is of considerable aid in persistent asthmatic states. Inhalation of 5 to 8 per cent carbon dioxide may be helpful in promoting expectoration and in increasing the cough reflex in status asthmaticus and in atelectasis.

Demerol, at first considered a very useful drug in asthma because of its antispasmodic and hypnotic actions, is now regarded by most observers as not much different from morphine in its disadvantages. Its objections are that it suppresses the cough reflex, it may be habit forming, and its effectiveness in asthma is not marked. Procaine intravenously has been recently advocated in serum sickness and urticaria. Since procaine allergy is not rare, it must be emphasized that such therapy can be distinctly dangerous.

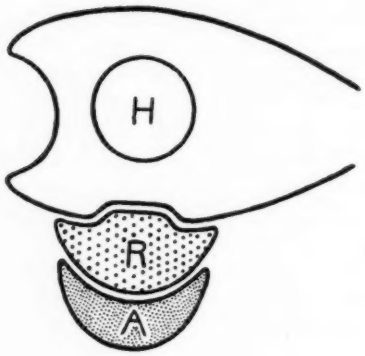
Ethylene disulphonate, claimed by the manufacturer to be very effective in allergic disease, has been found without demonstrable virtue.

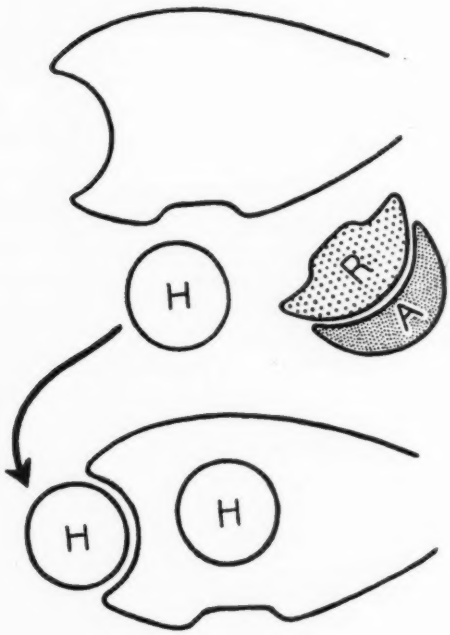
HISTAMINE RELEASE MECHANISM IN ALLERGY

Sensitized cell. Allergic cell has attached sensitizing antibodies—*reagins* (R). All cells, allergic or not, have *histamine* or its precursor (H) which causes no harm while within the cell.



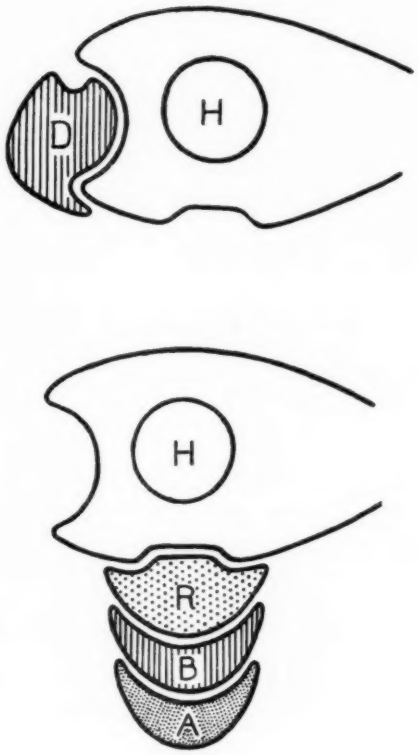
Antigen-reagin union. *Antigen* (A) unites with *reagin* (R) on the sensitized cell.





Release and action of histamine. Union of *antigen* and *reagin* causes release of *histamine* from within sensitized cell. This histamine is free to attach to receptors on adjacent cells, causing damage which results in allergic symptoms.

Figure 1



CONCEPT OF VARIOUS METHODS USED TO COMBAT HISTAMINE

Desensitization produces immune or *blocking antibody* (B) which attaches to reagin and prevents union of reagin and antigen.

Chemical block. Benadryl, pyribenzamine, neoantergan, and similar drugs (D)* attach to histamine receptors, thus blocking attachment of released histamine.

Figure 2

SYMPTOMATIC THERAPY OF HISTAMINE EFFECTS

Edema—corrected by: Epinephrine, ephedrine, and other sympathomimetics.
Smooth muscle spasm—corrected by: Aminophylline, epinephrine, nitrites, stramonium, caffeine.
Mucous gland dysfunction—corrected by: Iodides.
Excitation—corrected by: Sedatives.

*Note that the chemical block (D) has not the identical structure of histamine accounting for some of the additional effects from the antihistaminic drug.

Archibald showed that this drug intramuscularly was no more effective than injections of distilled water, both producing a slight nonspecific improvement in an occasional patient. Experimental and clinical data indicate that this substance is not antianaphylactic nor antiallergic. The Council on Pharmacy and Chemistry of the American Medical Association states that the existence of such a compound is open to serious doubt. It says further that "the theory of its dilution and its supposed part as an oxidative catalyst of carbohydrate metabolism is based on flimsy biochemical conjectures that have no proved connection with the mechan-

ism of allergy." The claimed dilution of 1^{10-15} is equivalent to 1 mg. of the substance in 250,000,000 gallons of water. At the prevailing price of the ampule 1 mg. of the chemical would be worth 5,000 billion dollars. Reports of favorable results are based on observations not eliminating the likely possibilities of spontaneous remissions, nonspecific effects of injecting distilled water, and psychogenic influence.

Anthallan is another alleged antiallergic remedy which created temporary excitement as a result of publicity given to a clinical report which lacked many of the features of controlled observation. The experience of a number of specialists in allergy indicates that this drug is of no value in allergic conditions. Furthermore, in preliminary experiments I have found that this drug has essentially no antihistaminic nor antianaphylactic properties.

Recently it has been reported that irradiation of the nasopharynx with the radium applicator was helpful in the treatment of the asthmatic child who had residual lymphoid tissue in the nasopharynx. This claim awaits confirmation.

POSSIBLE METHODS OF COMBATING HISTAMINE

Since Dale and Laidlaw in 1910 pointed out the similarity between manifestations of histamine shock and anaphylaxis in animals, and Lewis and Grant in 1926 called attention to the similarity between allergic and histamine wheals in man, considerable evidence has accumulated indicating the importance of the role of histamine in the mechanism of the allergic manifestations. It must be emphasized that although histamine release is regarded as an important part of this mechanism, there is increasing evidence that additional activities are also at play.

The mechanism of histamine release generally conceived is as follows: Histamine, or its precursor, resides within the cell, more in some tissues than in others. As long as histamine is not released from the cell it does not injure that cell or adjacent cells. The union of the antigen (such as pollen) with the reagin antibody on the cell of the allergic person results in a liberation of histamine (Figure 1). The latter not only injures that particular cell but also neighboring cells, and if the amount of histamine is sufficient it may affect remote tissues. Some of the known results of such histamine effects are contraction of involuntary muscle, increased capillary permeability, and stimulation of secretion of some of the excretory glands.

How, then, can we combat this histamine action? (Figure 2).

1. *By preventing the union of antigen and reagin.* The method long available is the process of desensitization by repeated and increasing injections of the specific antigen. It has been shown that such a procedure produces a new substance, the blocking antibody, which prevents the union of antigen and reagin. With the failure of this union no injury to the cell results and no histamine is released. The disadvantages of this method are, of course, the long continued treatment required and the fact that not all of the union of antigen and reagin can be blocked under all circumstances. It is possible that more perfect methods will be evolved to accomplish this effect, and perhaps other means than specific desensitization may be discovered to prevent the union of antigen and reagin.

2. *By increasing the tolerance to histamine.* This is theoretically possible by at least two mechanisms: (1) a general increase in resistance of the cells to chemical injury, including that due to histamine, and (2) a specific increase in histamine tolerance. It is well known that there is a variation in tolerance to histamine in different persons and in individuals of the same species of laboratory animal. It is not known, however, what constitutes the nature of this variation.

Attempts to increase histamine tolerance by specific immunization have not been successful. Although histamine injections have been and still are widely employed in allergic conditions there is no evidence that tolerance to histamine is built up in this manner. In the experimental animal, too, the preponderance of evidence

indicates that tolerance to histamine cannot be produced by subjecting the animal to repeated doses of the chemical, although temporary refractoriness may thus result. Furthermore, there is no basis for belief that allergic manifestations are produced because of a heightened sensitivity to histamine, and that proposed tests with histamine to classify people as allergic are fallacious.

In spite of all these considerations, it is possible histamine treatment may occasionally produce beneficial effects. It may possibly be of help in some instances of urticaria and cold allergy. Whatever good results are obtained must be explained on a basis other than desensitization to histamine.

Since histamine is a simple chemical substance and could not ordinarily be expected to produce antibodies for increased tolerance it was thought that by conjugating it to a large molecule, such as a protein, immunization to it could be made successful. The claims for this histamine-azo-protein were that it produced antibodies specific for the histamine portion of the conjugate in animals and in man, that it increased the tolerance to histamine and that it was effective in the treatment of allergic manifestations. Most critical experimenters and observers agree that there is no evidence that this substance increases the tolerance to histamine or that it has a specific antianaphylactic or antiallergic effect.

My own experience indicates that histamine-azo-protein does not have a high incidence of effectiveness in the treatment of allergic conditions, and when it does occasionally produce benefit it is probably due to the non-specific action of the foreign protein. Incidentally, it is important to call attention to the fact that the despeciated horse serum globulin which is part of the molecule of the histamine-azo-protein is still capable of producing severe allergic reactions in those who are sensitive to horse serum.

Another means of increasing the resistance of the cells to histamine is by competitive attachment of a less toxic chemical to the cell receptors available for histamine. This is regarded as the mode of action of the so-called histamine antagonists, benadryl, pyribenzamine, neoantergan, and similar drugs, as well as the amino acids, histidine, cysteine and arginine. These antihistaminic drugs will be discussed more fully in the last portion of the paper.

3. *By destroying the liberated histamine.* Since the discovery in 1929 by Best that some of the tissues contain an enzyme which is capable of destroying histamine, numerous efforts have been made to establish this enzyme histaminase as a therapeutic drug. The early claims of antianaphylactic and antiallergic action of this substance have been denied by later more critical experimental and clinical evaluations. It is true that histaminase when incubated with histamine for several hours will destroy moderate amounts of the latter. However, the conditions under which this drug would have to work in the living animal are apparently not the same. It has been concluded by the original discoverer of histaminase as well as by the Council on Pharmacy and Chemistry of the American Medical Association that there is no basis for its therapeutic use.

4. *By counteracting the effects of histamine.* Some of the known effects of histamine can be remedied by drugs having specific pharmacologic action. Vasodilating effects of histamine can be in large part corrected by various sympathomimetic or vasoconstrictor drugs such as ephedrine and epinephrine. Aminophylline and similar drugs relax the smooth muscle spasm and are most useful in asthma. Aminophylline orally is least effective, but is more useful when used in combination with ephedrine. Aminophylline intravenously (3-¾ to 7-½ gr.) is highly efficacious in many attacks of asthma. When intravenous medication is not practicable quite good results are frequently possible from the use of aminophylline suppositories (5 to 7-½ gr.).

Recently it has been claimed that aerosols of aminophylline solution are effective in some cases of asthma which do not respond to intravenous aminophylline. It should be remembered that aminophylline may be more helpful

in one stage (bronchospasm) of asthma while the vasoconstrictor drugs may be more effective in another stage (edema of the mucosa).

Among other effects of histamine action is the stimulation of secretory glands. Part of the respiratory discomfort in asthma is a result of bronchiolar obstruction by the tenacious mucus. The iodides constitute the ideal drugs in ameliorating that effect by stimulating the glands to produce a thin secretion.

NEW HISTAMINE ANTAGONISTS

Substances having a competitive action with histamine have been sought for a long time. The amino acids histidine, cysteine and arginine, were found to be antihistaminic and antianaphylactic, but the toxicity of the large doses necessary for these effects precluded their use. In France, long continued systematic attempts to produce synthetic antihistaminic compounds finally resulted in the clinically useful drug antergan (N′phenyl-N′benzyl-N-dimethylethylenediamine), which was later replaced by the less toxic neoantergan (N-p-methoxybenzyl-N-dimethylaminoethyl-a-aminopyridine). In Europe the latter is now the representative drug of the histamine antagonists. I have found neoantergan, which has been at my disposal for more than two years,* an active drug experimentally and clinically.

The antihistaminic drugs in present use in this country are benadryl (B-dimethylaminoethyl benzohydryl ether) and pyribenzamine (N′pyridyl-N′benzyl - N - dimethylethylenediamine). Their action has been discussed in considerable detail in many papers. Here I wish only to summarize their uses and limitations. In a large percentage of hay fever patients they are effective in the symptomatic relief of many of the symptoms, pyribenzamine being more consistent in its action. The hyperesthetic symptoms (sneezing and itching) are more often relieved than the edema (blocking). The symptoms early in the season, those in the milder cases and those occurring in patients who have had specific desensitization are more often benefited.

*First supplied to me through the kindness of Dr. B. N. Halpern and the Rhone-Poulonc Laboratories, Paris, France.

In the perennial allergic or vasomotor rhinitis, the incidence and degree of relief are not as great as in the seasonal; here, too, pyribenzamine has an advantage over benadryl. The dyspnea of asthma is not appreciably relieved by either of these drugs, although the spasmodic cough of the early stage of asthma may respond well. Now and then I have found that the combination of pyribenzamine with ephedrine or aminophylline or both produces an effective synergistic remedy in asthma.

Both drugs have a high incidence of effectiveness in the relief of the symptoms of urticaria, angioneurotic edema, drug rashes, dermographism, and the delayed "serum sickness" occurring after the administration of serum, penicillin or sulfonamides. The itching is benefited most, although the edema is usually also reduced and held in abeyance. When joint symptoms are present they are the manifestations most resistant to this therapy. In all of these patients it is necessary to give the drug frequently, usually every four to six hours, since its discontinuance results in a recurrence of the manifestations. There is no reason to believe that the duration of the disease is shortened by these drugs.

In eczema (atopic dermatitis) benadryl and pyribenzamine have been found effective in relieving itching in a large percentage of cases. In a few instances the prevention of the trauma from the cessation of the scratching favors the resolution of the dermatitis. Sometimes the itching of other conditions, such as pruritus ani, pruritus vulvae, and contact dermatitis and dermatomyositis, is also helped.

In patients having difficulty in avoiding constitutional reactions from desensitizing injections of antigen, I have found that the administration of pyribenzamine or other effective antihistaminic drug thirty to sixty minutes prior to the injection helped to diminish the intensity and the likelihood of a reaction. It should be emphasized that such inhibiting action is only moderately quantitative, that it does not always work, and that one can obtain reactions if the dose of the antigen is excessive. The discomfort, and particularly the itching, occurring

locally from the antigen injection in some instances may also be improved with these drugs. A dose of the histamine antagonist may also be helpful when one is compelled to subject himself to a known allergenic contact, such as a specific food or a dog. Other conditions in which these drugs may be useful at times are gastrointestinal allergy and allergic headache.

These drugs are usually given orally in 50 mg. doses to the adult. Pyribenzamine as a rule is tolerated in higher doses, and where needed can be frequently administered in 100 to 150 mg. amounts. Infants require 10 to 20 mg. of pyribenzamine, young children require 25 to 50 mg. doses, while older children tolerate and require adult doses. It is peculiar that not infrequently the child will tolerate the drug better than the adult. For young children or when small doses are used the drug may be taken dissolved in a sweetened vehicle. Because of the sedative action of these drugs it may be advisable at times to combine them with stimulants—ephedrine, amphetamine, or caffeine.

In special instances either drug may be given intramuscularly or intravenously in doses considerably smaller than those used orally. I have found that in some asthmatic patients an aerosol of pyribenzamine is effective in relieving the cough and dyspnea. In itching dermatoses, especially in eczema and in pruritus ani, I have utilized an ointment in which the pyribenzamine was incorporated. This has been of additional help with some patients who had partial relief from oral administration and has helped others who have not had much relief from the ingested drug.

The side actions of these drugs are not inconsequential. This is particularly true of benadryl which causes sleepiness in 50 per cent of the patients in many of whom it is of sufficient degree to make the use of medication inadvisable. Pyribenzamine also causes sedation, but does so less often and less intensively. Other effects which may be objectionable are dizziness, lassitude, disturbance in power of concentration, palpitation, fall in blood pressure, nervousness, insomnia, gastric irritation, and diarrhea. A dryness of the mouth and throat is not an infrequent complaint. Mental alertness is frequently diminished and it is important, therefore, to caution the patient about its use, particularly during his active hours.

In addition to benadryl, pyribenzamine and neoantergan we have been using experimentally and clinically several other drugs having similar actions. This is not the place to report in detail on these new drugs. A general statement, however, may not be amiss. Some of these drugs have an advantage over those on the market in that they are less toxic; others, although not having as high an efficiency index as pyribenzamine, are nevertheless the most effective drug for particular individuals; while still others are too toxic.

It is possible that further experience may show that some of these drugs are more useful in particular allergic manifestations. Some have promise of advantage because of longer duration of action. It is possible that drugs having additional activity other than antihistamine action may be developed; these may possibly be more effective in allergy.

There is considerable misunderstanding about the use of the antihistaminic drugs. Since their action is almost immediate it is not necessary to give these drugs for long periods to determine their effectiveness. If the drug is effective it can only help for a number of hours and must be repeated frequently. These drugs do not help all types of allergic manifestations nor all patients with any particular type of allergy. Neither are they effective to the extent of eliminating all symptoms of an allergic attack. They do not replace the more lasting benefit obtainable by successful specific avoidance or desensitization. Their toxic side actions frequently make them objectionable.*

*Two or three additional new drugs with which I have had considerable experience and which may be marketed soon, are worth mentioning here. Antistine (2-(N-phenyl-N-benzyl-aminoethyl-imidazoline), marketed in Europe, is only moderate in its antiallergic effects, but is relatively free from undesirable side effects. Thenylene or histadyl (N-(2-pyridyl)-N-(2-thenyl)-N′-dimethylethylenediamine), and chlorothen (N, N-dimethyl-N′-(2-pyridyl)-N′-(5-chloro-2-thenyl)-ethylenediamine) are potent antihistaminic and allergic drugs.

DIAGNOSTIC CLINIC

The Acute Abdomen

ROENTGENOGRAPHIC AIDS IN DIAGNOSIS

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THE WORD abdomen means "hidden" and indeed it seems quite appropriate since the diseased conditions of the abdomen are often baffling. Many diseases of the abdominal organs become chronic and can be investigated at leisure, but not infrequently abdominal conditions arise which require prompt diagnosis and immediate treatment. Roentgen examination offers a means by which such conditions often may be detected.

We have found four positions most valuable for the roentgenographic survey examination of the abdomen:

1. Anterior view of the chest, with the patient in the upright position. This examination is especially valuable for the detection of free gas below the diaphragm.

2. If the patient is too sick to assume the upright position, an anterior view of the abdomen may be made with the patient lying on the left side. This view serves especially well to show free gas in the abdomen and fluid levels in the hollow viscera. The right flank shadow may show exceptionally well and gas-distended loops of intestine are floated upward upon any exudate which may be present.

3. Anterior film of the abdomen with the patient in a prone position serves as a survey film to observe the size, form, and location of the abdominal organs, gaseous distended loops of bowel, fecal impaction, and biliary or urinary calculi. It also affords a good view of the flank shadows on either side of the abdomen.

4. A transabdominal view of the abdomen, with the patient lying on his back and the x-ray beam projected horizontally across the abdomen from side to side. This view gives the best impression of any abdominal exudate.

All of these views must be included in the examination in order that no vital information is overlooked. This technic alone often provides the information necessary for a correct conclusion as to the underlying pathology.

Rupture of a hollow viscus such as stomach or duodenum from peptic ulcer or of the small bowel from injury allows gas in the viscus to escape into the abdomen. It may be assumed that any gas free in the abdominal cavity is from this source. Gas rises to the top so that it will be found in the roentgenogram in a small collection under the diaphragm with the patient in an upright position. With the patient lying on the left side it will be found between the liver and lateral abdominal wall. When present, these findings may be considered as absolute indication of rupture of a hollow viscus. This sign is positive in 80 per cent of ruptured peptic ulcers; it is invariably present in ruptured typhoid ulcers of the small bowel. Prompt diagnosis of rupture of a hollow viscus is of utmost importance since the mortality of operative procedure rises markedly after the first few hours.

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Presented before the meeting of the Interstate Postgraduate Medical Association of North America, St. Louis, Missouri, October 14 to 17, 1947.

Many abdominal conditions are associated with gaseous distention of the intestines. Some of the conditions most frequently encountered in which dilatation is a prominent factor are:

(1) Intestinal obstruction (complete), (2) paralytic ileus (generalized), (3) localized paralytic ileus (due to infection or irritation), (4) localized spastic ileus, and (5) mesenteric thrombosis—arterial, venous.

LEROY SANTE

INTESTINAL OBSTRUCTION

When complete mechanical obstruction of the bowel occurs, vigorous peristalsis develops in an effort to overcome the obstruction. This involves the entire bowel both above and below the site of obstruction and is attendant with paroxysmal colic. Later these attacks subside and there is almost complete absence of any painful manifestation. Peristalsis empties the segment of the bowel below the obstruction, so that it is possible to have a bowel movement after obstruction has taken place. Once rid of its contents the distal segment of the bowel becomes flaccid and remains so; the rectum should be free from gas. The portion proximal to the obstruction, however, unable to rid itself of its contents, rapidly fills with gas.

WHERE the gas comes from, and the mechanism by which it forms, is not fully understood, but in all probability its chief source is from the products of putrifaction, and from interference with absorption by the blood stream. Roentgenologically, these gas-filled loops of bowel take on a characteristic appearance. By reason of its extreme dilatation the small bowel shows accentuation of the valvulae conniventes, giving rise to the so-called "herringbone" design. The loops of bowel arrange themselves back and forth across the abdomen forming a "stepladder" pattern, which is quite characteristic of the condition. These findings are best demonstrated in the anterior prone view of the abdomen.

Within a few hours after obstruction fluid is excreted into the bowel, giving rise to the roentgen sign of multiple fluid levels. This is due to partial interference with the blood supply squeezing the blood vessels between the intestinal coats. Large amounts of intestinal fluid are repelled back into the stomach by reverse peristalsis in an effort to rid the body of this toxic material and vomiting then begins in earnest. This culminates in fecal vomiting which is definite evidence of complete obstruction. Toxicity may become so great that the patient no longer feels sick but attains a deceptive feeling of well being. Continuous aspiration of stomach contents with Wangensteen suction apparatus may so eliminate both vomiting and toxicity as to mask the symptoms of the disease. Fluid excreted into the gas-filled bowel can be detected most readily as fluid levels in the upright, lateral decubitus and transabdominal positions. It occurs most extensively in obstruction but also may be present in paralytic ileus.

At times, the small bowel is so greatly distended that it may resemble the colon, and since it is very important to determine the exact location of the gas-distended bowel, barium enema

Figure 1. Air under diaphragm from rupture of a duodenal ulcer. This is a definite indication of rupture of a hollow viscus; it is a simple procedure, very accurate in its diagnostic significance, permitting early operative repair.

may be done to identify the involved portions. In small intestinal obstruction the flaccid condition of the large bowel will readily be noted on administering a barium enema. The calibre of the colon at first is very small, but as more of the barium enema is administered it will enlarge to its natural size. There is no danger to be expected from a carefully given barium enema and the information obtained is often decisive. At times it may even give evidence of the cause of the obstruction. After the examination is completed the barium enema may be siphoned off, often leaving in the colon only a negligible amount of barium mixture which should hardly interfere in any operative procedure.

The farther down the obstruction occurs in the gastrointestinal tract the less acute are the symptoms, so that complete obstruction from carcinoma may exist low down in the colon for many days without alarming symptoms. When the colon does become distended, as from volvulus, its enlargement is enormous. Volvulus of the large bowel is prone to occur in the sigmoid region due to redundancy of the sigmoid colon.

The presence of a palpable abdominal mass associated with the roentgen manifestation of obstruction always suggests the possibility of the mass as a cause of the obstruction. Constriction of the lumen of the bowel by a tumor mass may be converted into complete obstruction by impacted fecal material, and the mottled appearance of gas admixed with feces is quite characteristic. Barium enema examination will disclose whether the mass arises from the colon; if it arises from the small bowel it cannot be demonstrated in this manner.

It will be noted that the most outstanding symptoms of intestinal obstruction are: abdominal distention which is usually mild; vomiting which may be extensive or very mild, but it may be relied upon that vomiting should occur to some degree if obstruction is present. If fecal vomiting occurs it is in itself definite evidence of obstruction. Continuous Wangensteen drainage should not be instituted until the diagnosis is made since it may modify the clinical and roentgenographic picture and obscure the diagnosis. Pain at the outset may be intermittent and colicky in type, but never so severe or prolonged as to produce shock.

Since most obstructions encountered by the

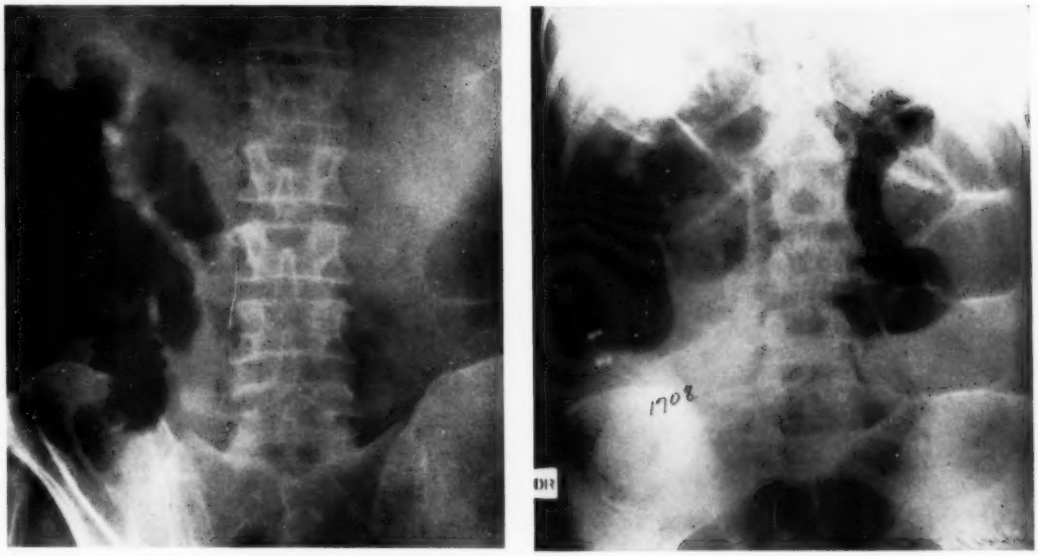

Figure 2 (left). Complete small intestinal obstruction following operative procedure. Note gas-filled loops of bowel but no gas in large bowel or rectum. (Right) Paralytic ileus; gas distributed throughout entire bowel, both large and small.

radiologist result from postoperative adhesions, the history of previous operation is of importance. In uncomplicated obstruction there is little, if any, fever.

PARALYTIC ILEUS

In generalized paralytic ileus due to nervous inhibition from peritoneal irritation or pleural involvement, the gaseous distention involves both the small and large bowel alike. The gas-filled loops of bowel do not show the same characteristic pattern or arrangement, but give a more redundant appearance leaving their impression on each other at their points of contact. The entire colon is filled with gas, and the rectum is greatly distended.

In intestinal obstruction, on the contrary, the distal portion of the bowel is empty and flaccid and the rectum does not contain gas. This is a point upon which the differential diagnosis between these conditions depends. Incidentally, this is likewise a good clinical point; in a complete intestinal obstruction the examining finger introduced into the rectum encounters an empty flaccid rectal pouch and the rectal mucosa falls limply about the examining finger, whereas in paralytic ileus the rectum is dilated with gas.

If paralytic ileus is caused by peritoneal infection, abdominal exudate will be present between the intestinal loops. This is best seen on the transabdominal view. If the process is an infiltrative one the lateral abdominal walls may be obscured and detail in the muscular structure may be lost.

The most outstanding clinical symptom in uncomplicated paralytic ileus is the pronounced abdominal distention; nausea and vomiting are usually entirely absent, and pain is not severe but is more in the nature of discomfort from gaseous distention. Vomiting is not a prominent symptom and is never fecal. Constipation is obstinate from the outset but fecal material may be syphoned off with an enema. In uncomplicated cases fever is not present, but if the condition is caused by or complicated with peritonitis, fever and other signs of infection will be present.

Figure 3. Intestinal obstruction from tumor of the cecum. The gas-dilated loops of small bowel show the "herring-bone" design and are arranged to use a barium enema to differentiate the large from the small bowel.

Localized paralytic ileus affecting only the loops of bowel surrounding a walled-off area of infection, simulate roentgenographically the gas-filled bowel seen in obstruction. As a rule, however, the loops of bowel are not as distended. Localized pain and extreme tenderness on palpation over the involved area is invariably present. There is no general distention but usually some interference with bowel action. Fever and other signs of infection are present.

Localized spastic ileus may produce a similar appearance showing varying amounts of gas-distended small bowel, without involvement of the colon. This, you will recall, is the criteria for diagnosis of small bowel obstruction and at times, differentiation may be very difficult. In spastic ileus of this type, however, the intestinal loops do not show the extreme dilatation seen with mechanical obstruction.

Localized spastic ileus occurs as a reflex response to abdominal pain such as passage of a calculus, ureteral catheterization, or injury to the peritoneum; the presence or absence of pain then becomes an important differential symptom. Pain from rupture of a tubal pregnancy results in this type of intestinal reaction; at the outstart there is no fever. Later, however, if hemorrhage or infection ensues, peritonitis develops with generalized intestinal dilatation and peritoneal exudation with fever.

One of the most difficult conditions to diagnose associated with gaseous distention of the bowel is mesenteric thrombosis. This produces gaseous distention of the small bowel and even varying amounts of the colon (up to the mid-transverse colon if the superior mesenteric artery alone is involved; entire intestinal tract if both mesenteric arteries are thrombosed). Barium enema may show dilatation of the colon up to the mid-transverse portion without obstruction or other cause.

There are two points most helpful in making the diagnosis; first, mesenteric thrombosis is almost always associated with sudden severe pain even from the very outstart. The pain is so persistent and severe that it produces an extreme degree of shock; second, it is frequently associated with chronic valvular heart disease or other condition of the circulation. Gaseous distention and pain are most pronounced with the arterial mesenteric thrombosis, while with venous thrombosis, especially at the onset, no demonstrable gas-filled loops may be present.

We have endeavored to show how a careful

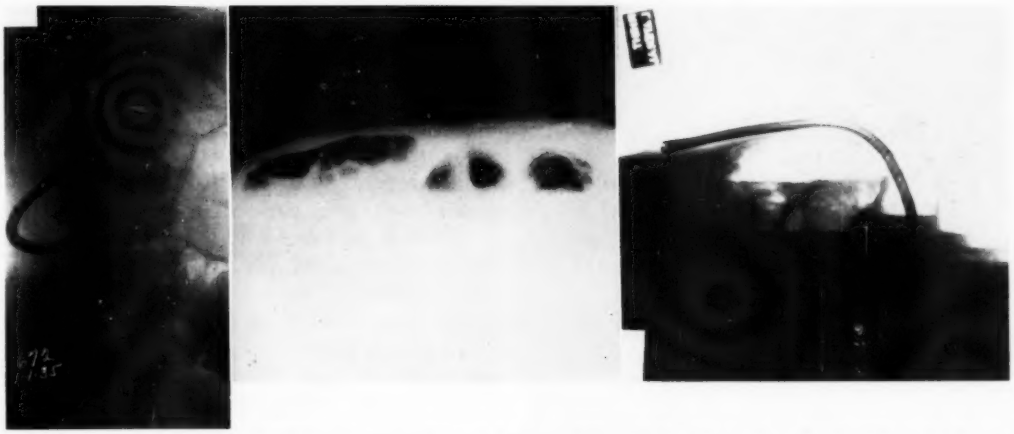

Figure 4. A. Paralytic ileus showing gas-distended loops of bowel affecting all of the intestines, both small and large. The rectum is filled with gas. B. Lateral decubitus position showing fluid levels and exudate between coils. C. Transabdominal position best for showing abdominal exudate.

analysis of the roentgen findings, correlated with certain clinical signs and symptoms will serve to establish the diagnosis in cases where gaseous dilatation of the bowel is a prominent symptom. We have emphasized the use of a barium enema in determining the presence or absence of large bowel involvement in the analysis of the roentgen findings.

OTHER acute abdominal conditions which may or may not be associated with gaseous distention of the bowel will be briefly considered: (1) congenital atresia of bowel, (2) intussusception, (3) carcinoma of the colon suddenly obstructed by fecal matter, (4) rupture of diverticulum of colon, and (5) subphrenic abscess.

Congenital atresia of the bowel usually does not give acute symptoms unless it is complete. If this is the case, the picture produced is similar to small bowel obstruction from any other cause —there should be gaseous dilatation above the point of atresia and the bowel should be empty below—there should not be any gas in the rectum.

Intussusception produces acute abdominal pain, nausea, severe prostration, and at times bloody mucus stools. Abdominal palpation or rectal examination may disclose this to be the advancing head of an intussusception. Unless the intussusception causes intestinal obstruction, gaseous dilatation will be absent. Barium enema, however, will readily disclose the crescentic rounded outline of the barium as it spreads out over the advancing head of the intussusception. Ringlike shadows within the dilated bowel are characteristic of this condition.

Carcinoma of the colon, as insidious as it usually is, may assume very acute manifestations if the small remaining lumen is suddenly occluded by fecal material. Barium enema examination discloses the carcinomatous character of the lesion and may even dislodge the fecal material and open the obstruction.

Rupture of a diverticulum of the colon usually occurs in the sigmoid region, the most frequent site of diverticulitis of the colon, resulting in severe acute abdominal symptoms. Such ruptures are usually not attendant with gas free in the abdomen. The prevalence of diverticulitis of the sigmoid in older individuals (referred to clinically as left-sided appendicitis) is well known so that the examiner may be on his guard in giving cathartics or enemas. If the diagnosis is doubtful or if barium enema is given, usually only a very tiny amount is seen extending beyond

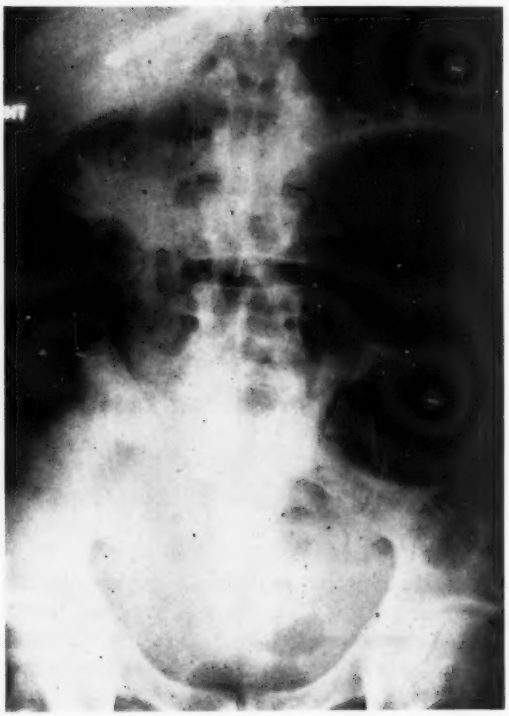

Figure 5. Wherever there is intense pain the findings must be analyzed carefully. Ruptured tubal pregnancy with pelvis filled with blood prevented filling of rectum by gas and gave pattern of possible intestinal obstruction when it was really due to paralytic ileus. Mesenteric thrombosis may also give confusing picture.

the confines of a diverticular sac. In most cases an inflammatory mass has already formed, well walled off by the surrounding tissues.

Subphrenic abscess—If a subphrenic abscess is attended with gas from a gas-producing organism, then x-ray examination in the upright and lateral decubitus positions will readily disclose the gas with a fluid level. In most instances, however, there is no associated gas; there is merely immobilization of the diaphragm in a high position. Such splinting of the diaphragm is merely a defense reaction against pain since either the visceral pleura or peritoneum must be involved to cause such reaction. The immobilization of the diaphragm in a high position in itself does not imply subphrenic abscess for such reaction uniformly follows operative procedure or any other insult to the parietal pleura or peritoneum.

There is only one way in which infection of the subphrenic space can be demonstrated and that is by the aid of artificial pneumoperitoneum. A few pumpsfull of air in the abdominal cavity is all that is required. In the upright or lateral decubitus position the air thus introduced will pass freely into the subphrenic space if it is normal and uninvolved, whereas, if it is the site of inflammation the adherence of the diaphragm to the upper surface of the liver or spleen will prevent access of the air to this region.

DEEP-SEATED infection frequently produces sympathetic effusions in adjacent synovial cavities, and subphrenic abscess may thereby give rise to basal exudates in the pleural cavity. Fluid aspirated in such cases is frequently clear but it usually contains polymorphonuclear leukocytes. In such cases artificial pneumoperitoneum is necessary to determine if the pleural effusion is associated with a pyogenic infection below the diaphragm or if it is a simple pleural exudate. A great deal depends upon the outcome of the examination.

This method of examination has been urged for many years but has not come into general use. Surgeons seem reluctant to use artificial pneumoperitoneum in the presence of possible infection in the subphrenic region but we have never, in over twenty years experience, seen it cause any difficulty or spread of the infection. The small amount of air used exerts such a minimal amount of pressure that the most delicate adhesions remain unaffected. The information afforded by this method far outweighs any theoretical disadvantage.

DIAGNOSTIC CLINIC

The Xiphosternal Crunch

ITS RECOGNITION AND UNFORTUNATE ROLE IN LIFE INSURANCE AND EMPLOYMENT REJECTIONS

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It is a great tragedy that persons in perfect health are rejected when applying for employment, for life insurance, or for service with the armed forces merely because of a heart sound that has no pathologic significance.

In a considerable proportion of individuals, both well and sick, a crunching sound can be heard over the lower portion of the sternum and over the xiphoid cartilage, slightly to their left. In almost half the cases in which it is present, this xiphosternal crunch is so faint that it may not even be noticed. In the remainder, however, it is fairly loud, and in about one-fifth of the cases its presence is very marked. Many physicians, mistaking it for the murmur of valvular or congenital heart disease or for pericardial friction, subject their patients to prolonged unnecessary treatment and restriction of activity. On observing it, insurance examiners have rejected normal applicants or raised their rating, company doctors have denied employment to persons in good health, and medical officers have refused to admit to the armed services men and women who have no actual physical defect.

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My attention was first directed to this sound forty-five years ago, when I was an assistant in the medical dispensary of the University of Pennsylvania Hospital. I heard a peculiar heart sound that I could not identify and which my superiors could not explain. When invited to present a paper before the Lehigh Valley Medical Society in 1903, I spoke on "A Xiphosternal Crunching Sound with a Report of Six Cases," and published the paper in the American Journal of the Medical Sciences. In reviewing the medical literature of the previous eighty years, I found no description of the sound in any book on general medicine. However, I did find reference to it in one book on physical diagnosis and in several books and articles on the heart.

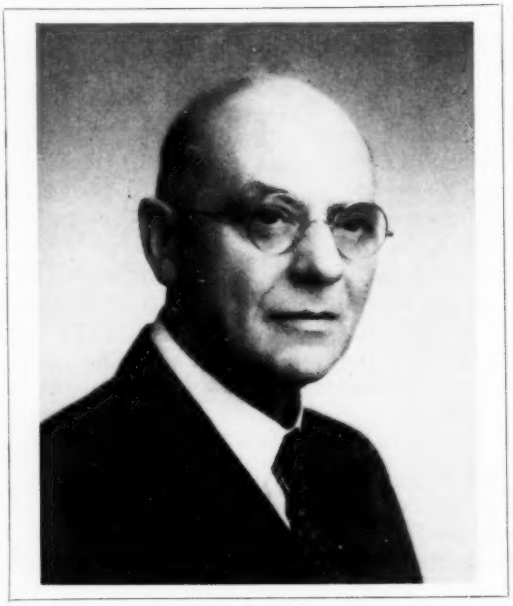
I have never been able to connect the crunch with any clinical symptom or pathologic condition, although in 1909 I made and published an analysis of sixty-three cases. Since then I have observed the phenomenon in hundreds of my patients, some of whom were rejected for military service in World War I because of it. It was not until four or five years ago, however, when I served on the heart and lung section of the medical examining board of an Armed Forces Induction Center, that I had an opportunity to examine the hearts of large numbers of supposedly healthy individuals. The xipho-

sternal crunch was audible in 17.8 per cent and I found that, for this reason, men with normal hearts were being rejected by able and competent internists and cardiologists. On questioning those presenting this sound, I learned that some of them had been rejected for employment or life insurance and that others had been treated for a cardiac lesion at a great expense of time and money.

I BEGAN to keep notes on all those showing the crunch, and when I had examined 5,000 men, I studied these notes and published the results in the American Journal of the Medical Sciences. Before writing that article about two years ago, I examined most of the books and articles on physical diagnosis, cardiology, and heart sounds published during the previous 125 years. I discovered thirty-one references to what seemed to be the xiphosternal crunch and ten references to what may have been that sound.

It seemed to me that many writers who discussed the murmur of relative or functional tricuspid insufficiency had mistaken the xiphosternal crunch for such a murmur, especially those who regarded incompetency of the tricuspid valve as a common occurrence. I also feel that the cardiorespiratory murmur about which so many authors write is, in many instances, the xiphosternal crunch. Many cardiologists mention only the cardiorespiratory murmur when referring to accidental murmurs. The leaflet on "Examination of the Heart," published by the American Heart Association, describes temporary systolic murmurs produced by infections or other causes of ill health, which sometimes are apical, at other times heard over the whole precordium, and sometimes localized to the left of the sternum or to its lower portion.

Why such a common phenomenon is seldom noticed and why it is ignored by most writers on cardiology, medicine, and physical diagnosis is difficult to explain. One can understand how it would be missed by cardiologists who listen only at the apex and at the base of the heart and fail to include the xiphoid cartilage. It is quite possible that expert cardiologists, knowing the crunch has no pathologic significance, do not hear it at all, having trained themselves to recognize only pathologic sounds and to ignore all others.



MYER SOLIS-COHEN

How can one expect a physician to be on his guard against a heart sound about which he was taught nothing in medical school and which is not mentioned in his books or journals? It is not surprising that when many hear the xiphosternal crunch they regard it as evidence of cardiac pathology.

The xiphosternal crunch, when fairly loud, is not difficult to recognize. It has a characteristic crunching, creaking, rubbing, grating, scratching, brushing, or clicking sound. Schwab, Smiley, and Meyn describe it also as a spitting sound. Other adjectives that have been used to describe it are rasping, buzzing, flapping, clacking, whizzing, tapping, vibrating, high-pitched, rough, short and quick, superficial, dry, stiff, harsh, short and rough, musical, and extracardial. It has been called a chisel-sound, a metallic click or tinkling, a

creak, a gastric tinkle, an after-tone or echo, a reduplication, a coin sound, the word "ching," and a murmur. I have compared it to the sound made by a foot crunching in soft snow. Others have compared it to the sound made by striking the clasped hands against the knee, by a chisel or short plane used forcibly across the end of a piece of timber, by a file drawn over wood, by the rubbing together of two pieces of velvet, by drawing a cork out of a bottle, by allowing a stiffly starched cuff to rub slightly against the other while they are on the wrist, by the knock of a motor, by the creak of leather of a new saddle under the rider, and by placing the palm of the hand over the ear and percussing the occiput with the end of the index finger.

The variations represent how the crunch sounded to different observers as well as in different subjects. Despite its variants, the sound can be recognized easily when distinct, although when faint it may be unnoticed by an ear not trained to detect it. However, when faint, it is seldom mistaken for a pathologic sign. It has a superficial quality, as if produced close to the ear or occurring outside the heart.

The crunch has accompanied systole in most of the cases I have examined, although others have heard it also in diastole, and frequently becomes more pronounced when the subject leans forward. Its intensity occasionally increases with exercise, nervousness, excitement, or fear. In many instances the sound diminishes or even disappears when the patient lies down. Pressure of the stethoscope has not been shown to influence the sound.

The xiphosternal crunch should not be confused with a cardiorespiratory murmur, as it occurs not only during breathing, but also when the breath is held. Its intensity sometimes varies with the different phases of respiration and it is frequently heard best at the end of expiration. If the patient breathes slowly and deeply, a cardiorespiratory murmur will often disappear completely at some point in the respiratory circle, while the xiphosternal crunch will not.

The location of the crunch is typical. The maximum intensity of the sound will almost always be found over the lower end of the sternum and over the xiphoid cartilage and an inch or so to their left. A loud crunch is often transmitted to the left, in a few instances as far as the mid-precordium and occasionally even to the apex of the heart. In these cases it is easily mistaken for the murmur of mitral insufficiency. However, one has only to carry the bell of the stethoscope to the right as far as the sternum to note a gradual increase in intensity if the sound is a crunch, and a gradual diminution if the origin is in the mitral valve.

On the contrary, when the stethoscope is moved to the left, the crunch will diminish and disappear, for it is never heard in the axilla. If the sound heard over the sternum has its origin in the aortic or pulmonic valve it will increase as the stethoscope is moved up from the ensiform cartilage to the base of the heart, while the xiphosternal crunch will diminish.

The apical systolic murmur, considered a normal phenomenon in young persons, is of a blowing quality and, unlike the crunch, is not constant from day to day. Organic systolic murmurs at the apex are rough, not crunching, and do not seem superficial. They are sometimes accompanied by a thrill, which does not occur with the xiphosternal crunch. The latter has been mistaken for the murmur of congenital heart disease, but its character and location should serve to differentiate it.

The superficial and rubbing quality of the xiphosternal crunch has resulted in its being diagnosed occasionally as a pericardial friction, but the latter has a to and fro sound occupying both systole and diastole.

Although they have the same location, the xiphosternal crunch should not be confused with the murmur of tricuspid insufficiency, whether organic, relative, or functional, owing to the absence of the symptoms usually associated with the latter, such as pulsation in the vessels of the neck and an enlarged, tender, and pulsating liver. I believe that the common diagnosis of incompetence of the tricuspid valve is in many instances the xiphosternal crunch.

Aids in differentiating the xiphosternal crunch from organic murmurs are the absence of a cardiac history or of cardiac symptoms, the presence of a normal cardiac rhythm, and a heart of normal size. In doubtful cases the x-ray and the electrocardiogram may also prove helpful.

The cause of the xiphosternal crunch is not known. Many explanations have been offered, suggesting its origin in the heart, in the pericardium, or in the outside tissues. Among the less fantastic causes offered are vibrations of the chordae tendineae produced by imperfect contraction of their muscular attachments and permanent lack of tone. Some regard the phenomenon as a valve sound, a cardiomuscular sound, or a drawing out of the scratch of the second aortic sound.

The causes believed to be in the pericardium include a fibrous patch or white pericardial patch or "milk spot," a rubbing of the visceral over the parietal lamina, and localized precordial roughening.

Those who place the cause outside the pericardium suggest friction of the heart against the chest wall, crowding of the heart—enlarged or distended with blood—in the inferior mediastinum, downward displacement of the heart due to emphysema, mediastinal emphysema—the air in the tissues causing a crepitant sound, movement of the xiphoid, changes in the tension of the loose cellular tissue in the sternoprecordial ligament which binds the anterior surface of the pericardium to the posterior thoracic wall, and gastric resonance imparted to the right ventricle of the heart through the diaphragm. Schwab, Smiley, and Meyn proffer the explanation that the sound is produced by movement of the seventh costal cartilage at the point of articulation with the sternum and the xiphoid process. All observers are in agreement that the xiphosternal crunch has no pathologic significance.

Ninety-one years ago, Brown recorded that "a chisel sound at the lower end of the sternum is of frequent occurrence in persons who are in good health in all respects excepting dyspepsia."

In his book on "The Diagnosis of Diseases of the Heart and Thoracic Aorta," published in 1892, Sansom wrote: "There can be no doubt that short, rough, systolic, seemingly very superficial sounds are often to be heard over the situation of the right ventricle in conditions which deviate in no notable way from the standard of health."

William Osler, discussing Hare's paper on "An Undescribed Cardiac Sound" at a meeting of the Association of American Physicians in 1901, said: "There is a distinct difference in the majority of healthy hearts between the first sound over the apex and that as you move toward the sternum, a more crunching sound, which is peculiar and remarkable."

Colbeck in his book on "Diseases of the Heart," published that same year, stated that a peculiar form of friction sound is sometimes heard over the right ventricle at the level of the fifth and sixth intercostal spaces, close to the left sternal edge and over the base of the ensiform cartilage, often present under apparently normal conditions.

Thirteen years later Blumer wrote: "This peculiar quality of the heart sounds underneath the sternum and in its neighborhood seems to be worthy of emphasis because the phenomenon is a normal rather than a pathological one, and because under certain conditions it may be mistaken for a pathological sound and give rise to errors in diagnosis. I have noted the almost constant presence of the sound in all sorts of cases for a number of years."

King in 1919 said that the crunch is a common phenomenon of the normal heart and may be observed in most hearts, particularly in the leaning forward position. It was observed commonly by him in normal soldiers and in men with irritable hearts. King repeated this information in "The Practitioner's Library of Medicine and Surgery" in 1932, in "The Cyclopedia of Medicine, Surgery and Specialties" in 1939, and in Stroud's "The Diagnosis and Treatment of Cardiovascular Disease" in 1940.

Norris wrote in 1924: "In a considerable

number of perfectly healthy individuals the heart sounds heard just over the ensiform cartilage and in its immedate vicinity have a peculiar harsh, scratching, scraping, or crunching quality resembling a pericardial friction sound."

Schwab, Smiley, and Meyn, in a recent investigation as yet unpublished, found the sound in 3.3 per cent of more than 3,000 Army separatees.

I am not the only one who has seen the xiphosternal crunch diagnosed as an organic murmur. Similar mistakes were reported by Laennec in 1826, Gairdner in 1862, Sutton in 1867, Broadbent in 1897, Benedict in 1910, Blumer in 1914, King in 1919, 1932, and 1939, and Norris in 1924.

Whether you examine applicants for life insurance, or for employment, or the armed forces, or have a patient in your office, you ask questions about all the diseases he has had. If he has never had growing pains in childhood, rheumatism, pains in the joints or muscles, shortness of breath or palpitation on exertion, swelling of the feet, signs of heart disease, or heart consciousness, you consider him a good risk. You get out your stethoscope and listen over the apex; you listen again and you do not hear anything abnormal; you listen at the aortic and pulmonic areas. Fine! Too many cardiologists stop there.

THE CARDIOLOGIST in charge of the cardiac ward of one of our naval hospitals stated that he never listened at the xiphoid cartilage when he examined a patient. When an examiner listens at the xiphoid cartilage he hears a peculiar sound. Sometimes he finds this sound at the apex, and because that is the only place he listens, he calls it a systolic apical murmur. If he would carry his stethoscope over further, he would find the sound getting louder and louder with a very definite crunch, and if he went on over to the left it would disappear. In systole, of course, he would hear it. He would get the borders of the heart and find that they were normal; he would feel the pulse and that would be normal. He would have the man lie down, expecting the murmur to be louder in some cases, but on the contrary, it would become softer, and perhaps disappear. He would have the patient lean forward and in some cases he would find it getting louder. He would find by these few little manipulations that it is not a cardiac murmur.

It is difficult to understand why books on physical diagnosis, the modern books on cardiology, with the exception of Stroud's, and articles on heart sounds, especially peculiar heart sounds, make no mention of the xiphosternal crunch. Two prominent cardiologists, in two articles on peculiar heart sounds, mentioned about twenty but never this one.

It is a peculiar heart sound, difficult to understand, and seemingly harmless. Some of my patients were rejected in World War I, but I did not fully realize the importance of the situation until I served in the heart and lung section at a large induction center in Philadelphia, and again in a smaller one in Camden, and found capable doctors rejecting men because of the xiphosternal crunch. Although none of these doctors had heard of it, they were all interested, and those who came on the days I was there became very well acquainted with it and could detect it as well as I could.

When men who had been rejected on a day when I was not there were reexamined, I found that all they had was a xiphosternal crunch; it was then that it seemed to me very important that it be brought to the attention of the profession. For this reason I took notes on all the patients, because before that time I did not realize that the sound occurred in normal people. Most of the people who come to my office are sick and I had been trying to find the pathologic condition associated with the sound. It was somewhat of a revelation to find that so many of these so-called normal hearts (I say "so-called" because we all know that those examined at the induction boards were not all really normal) showed this sign. It seemed very important, and that is why I deemed it necessary to bring it to the attention of the medical profession.

Cholecystography in Diagnosing Small Calculi and Stones

ADOLFO J. BURLANDO*

CENTRAL MILITARY HOSPITAL, BUENOS AIRES, ARGENTINA

CHOLECYSTOGRAMS made in the usual prone position often fail to reveal small stones or tumors when the gallbladder fills completely with the dye.

The density of the vesicular shadow may totally obscure small cholesterin calculi or small intravesicular tumors.

For more than ten years we have used the same procedures for the roentgenologic study of the gallbladder as for the duodenal bulb: fluoroscopic examination and instantaneous serial roentgenograms.

Fluoroscopic examination permits us to localize the vesicular shadow with relation to neighboring structures, to manipulate or compress the gallbladder region and obtain the clearest view.

In the standing position, concentrated bile and iodine is heavier than cholesterin concretions, which consequently are suspended, and produce a clear, translucent band that is very easily interpreted.

We have selected from our files some cholecystograms which demonstrate the great diagnostic difficulties with the usual roentgenograms, and the clarity with which the small suspended cholesterin calculi and the papillomas are revealed in the instantaneous roentgenograms that were made in the upright position with compression.

Figure 1 (upper left). Radiographs in prone decubitus. No calculous images are perceived.

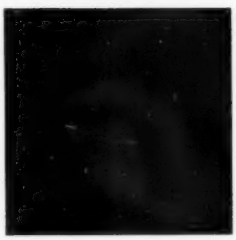
Figure 2, A and B (lower left). Same patient: radiographs in upright position, delayed. Suspended cholesterin calculi.

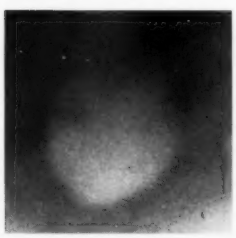
Figure 3 (upper right). Cholecystograph in prone decubitus. Spotted vesicle.

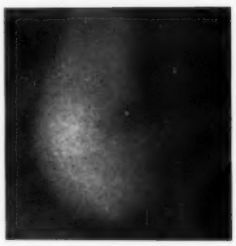
*Chief of Department of Electroradiology, Central Military Hospital, Buenos Aires, Argentina.

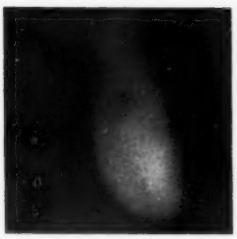
Figures 4 and 5, A and B (top). Cholecystographs of the same patient as in Figure 3 in standing position with distinct inclinations. The plane of the calculi is maintained horizontal.

Figure 6 (left). Cholecystograph in prone decubitus. Same radiotranslucent image.

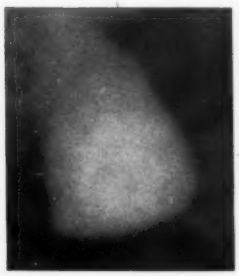


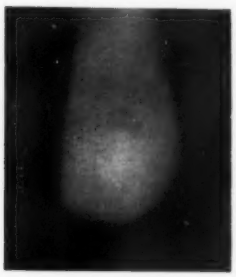






Figures 7, 8, and 9 (left and below). Study of the same vesicle in standing position and in different position grades of rotation. The papilloma is clear and always in the same position relative to the vesicular walls.





RADIOGRAPHIC FACTORS

Radiographs in prone decubitus: diaphragm P. B. Kv. 70-60 plus 70 distance 1 meter. Picture Eastman Blue Brand. Double (filter, screen) reinforced.

RADIOGRAPH DELAYED

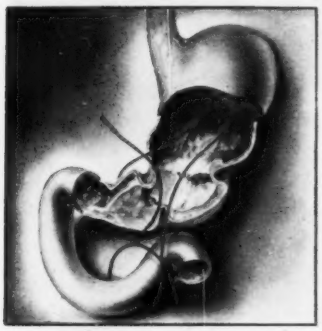
Upright position. Mean distance 70 centimeters. Kv. 65-70 plus 40 (300 milamp.). Double filter (movable, continuous). Eastman picture. Revolving tube of anode.

Transthoracic Vagotomy for Peptic Ulcer

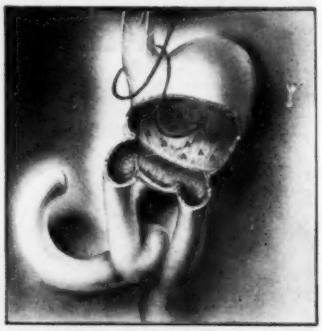
A scientific exhibit from Grimson, K. S., Baylin, G. J., Taylor, H. M., Hesser, F. H., and Rundles, R. W., of the Duke University School of Medicine, Durham, N. C.

THERE ARE TWO IMPORTANT MECHANISMS THAT MAY INFLUENCE THE DEVELOPMENT AND COURSE OF DUODENAL OR GASTRIC ULCER BY ALTERING MOTILITY AND SECRETIONS OF THE STOMACH:

THE FIRST OF THESE MECHANISMS IS HORMONAL.



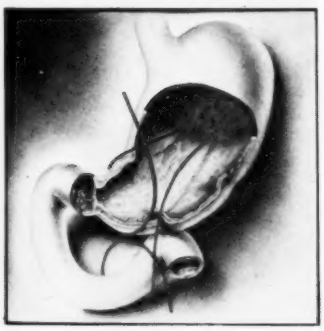
SUBTOTAL GASTRIC RESECTION AFFECTS THIS MECHANISM BY REMOVING THE ANTRUM AND EXCLUDING THE DUODENUM



TRANSTHORACIC VAGOTOMY WAS FIRST CONSISTENTLY AND EFFECTIVELY EMPLOYED FOR PEPTIC ULCER IN 1943 BY L.R. DRAGSTEDT. IT HAS BEEN USED IN DUKE HOSPITAL SINCE JUNE 1944.

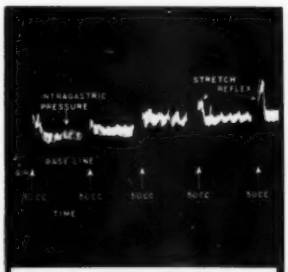
THE SECOND OF THESE MECHANISMS IS NERVOUS.

TRANSTHORACIC VAGOTOMY THEORETICALLY BLOCKS NEUROGENIC, PSYCHOGENIC OR REFLEX STIMULI.

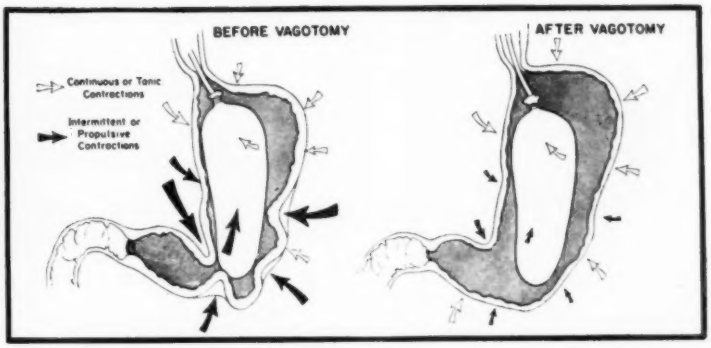


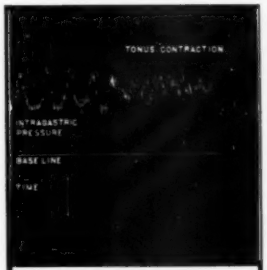
TRANSTHORACIC VAGOTOMY HAS BEEN PERFORMED UPON 57 PATIENTS. FOLLOWED 9 TO 36 MONTHS.

VAGOTOMY ALTERS ACTIVITY OF THE STOMACH AS JUDGED BY BALLOON

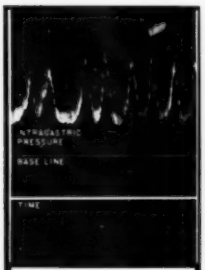


Patient A7 Stretch reflex before vagotomy



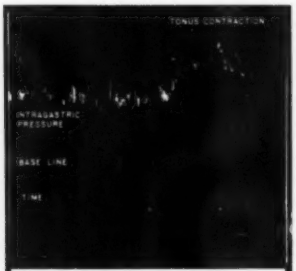


Patient A3 "Tonus" contraction before vagotomy.



Patient A24 Typical intermittent pressure waves before vagotomy.

Patient A20 Typical low intermittent pressure waves 4 months after vagotomy.



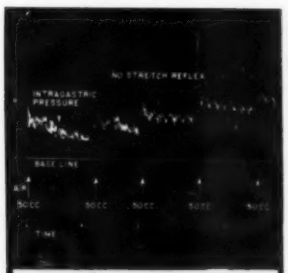
Patient A9 "Tonus" contraction 3 months after vagotomy.

CHANGES OF INTRAGASTRIC PRESSURE BEFORE AND AFTER VAGOTOMY

(Balloon filled with 300 cc. of air and pressures recorded by a Bromoform Manometer)
(Readings are converted to cm. of water)

	Before Vagotomy	1-3 Wks. After Vagotomy	5 Wks.-4 Mos. After Vagotomy	4 Mos.-2 Yrs. After Vagotomy
Group A ● Patients Tested	20	27	14	6
Average Resting Pressure "Tone Base Line"	4.6 cm.	7.5 cm.	8.1 cm.	8.7 cm.
Average Excursion Above Resting Pressure	11.8 cm.	0.8 cm.	2.4 cm.	1.2 cm.
Group B ● Patients Tested	1	1	2	1
Average Resting Pressure "Tone Base Line"	4.1 cm.	6.4 cm.	8.1 cm.	7.0 cm.
Average Excursion Above Resting Pressure	8.7 cm.	1.2 cm.	1.7 cm.	7.5 cm.
Group C ● Patients Tested	2	2	3	1
Average Resting Pressure "Tone Base Line"	7.5 cm.	6.9 cm.	8.7 cm.	9.9 cm.
Average Excursion Above Resting Pressure	8.7 cm.	1.5 cm.	4.6 cm.	7.5 cm.
Group D ● Patients Tested	1	2	3	0
Average Resting Pressure "Tone Base Line"	7.0 cm.	7.0 cm.	9.3 cm.	
Average Excursion Above Resting Pressure	4.1 cm.	0.6 cm.	1.5 cm.	
Group E ● Patients Tested	6	7	4	1
Average Resting Pressure "Tone Base Line"	4.1 cm.	8.1 cm.	8.7 cm.	9.3 cm.
Average Excursion Above Resting Pressure	12.8 cm.	0.9 cm.	1.0 cm.	0.6 cm.

Pain with contractions and stretch reflexes were occasionally observed before but not after operation. Slow "tonus" contractions were observed occasionally before and after vagotomy.



Patient A7 No stretch reflex 3 months after vagotomy

Patient W.S. 10 days after vagotomy immediately after taking barium.

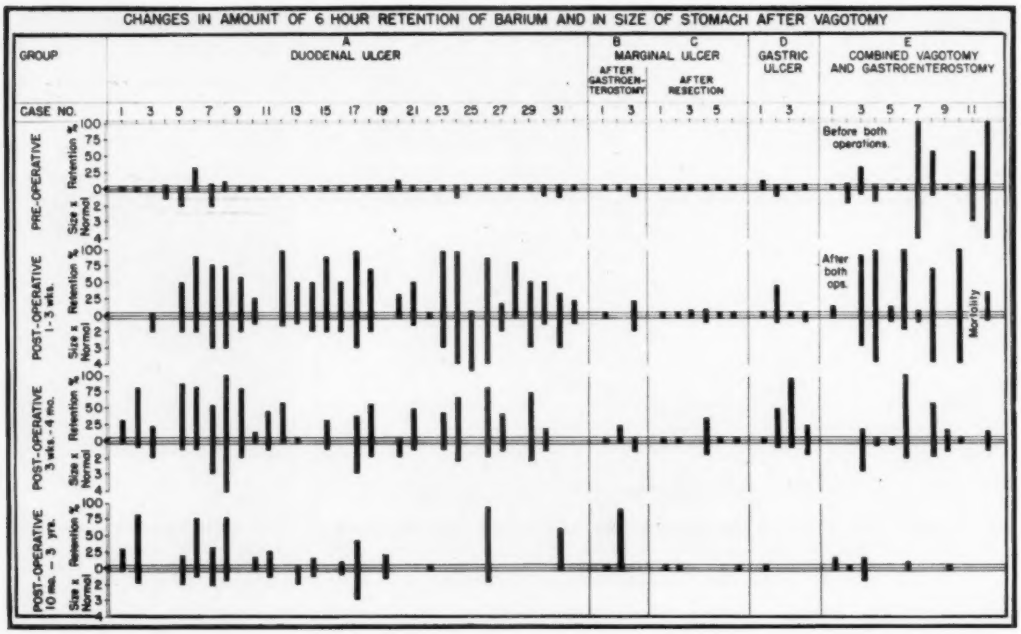
Patient W.S. 10 days after vagotomy 6 hours after taking barium.

VAGOTOMY ALTERS ACTIVITY OF THE STOMACH AS OBSERVED BY X-RAY

EXAMINATION OF STOMACH BY X-RAY AFTER BARIUM MEAL

Number of Patients	BEFORE VAGOTOMY						AFTER VAGOTOMY (1 Week to 4 Mos.)					
	Duodenum		Peristaltic Waves				Peristaltic Waves				Duodenum	
	Visualized	Crater	Hyperactive	Active	Weak	Absent	Active	Slow	Weak	Absent	Visualized	Crater
32 With Duodenal Ulcers	32	16	8	24			6	7	16	1	19	1
3 With Enterostomy Stoma Ulcers	3			3					2	1	1	
6 With Resection Stoma Ulcers					1	4			1	4		
4 With Gastric Ulcer	4			3	1		2	1	1		4	
12 With Combined Operations	9	8	5	3	2	1	1		6	3	2	

CHANGES IN AMOUNT OF 6 HOUR RETENTION OF BARIUM AND IN SIZE OF STOMACH AFTER VAGOTOMY



VAGOTOMY ABOLISHES ULCER PAIN EVEN IMMEDIATLY AFTER VAGOTOMY AND BEFORE ULCERS HAVE HEALED.

PAIN PATHWAYS ARE NOT INTERRUPTED BY VAGOTOMY:

1. Spinal anesthesia high enough to block the splanchnic pathways relieves ulcer pain even though the vagus nerves are intact.

2. Stimulation of the vagus nerves in the lower chest in 2 patients and below the diaphragm in 2 others during operation under spinal anesthesia did not produce abdominal pain.

VAGOTOMY PROBABLY RELIEVES ULCER PAIN BY REDUCING GASTRIC MOTILITY. THIS RELIEF MIGHT BE EFFECTED BY DIMINISHING IRRITATION OF THE ULCER - PRODUCED BY FORCEFUL THRUST OF GASTRIC CONTENT AND BY REDUCTION OF PAINFUL SPASM OF GASTRIC SMOOTH MUSCLE. THIS HYPOTHESIS IS BASED UPON THE FOLLOWING OBSERVATIONS:

NONSPECIFIC EFFECTS OF ANESTHESIA OR OPERATION DO NOT ACCOUNT FOR RELIEF OF PAIN:

1. One patient, after an hour of ethylene ether anesthetic without operation, promptly experienced pain when acid was introduced into the stomach.

2. Several of the patients gave a history of previous appendectomy or cholecystectomy with only temporary relief of pain.

ALTHOUGH ACIDITY OF THE SECRETIONS OF THE STOMACH IS USUALLY REDUCED BY VAGOTOMY, THIS IS NOT THE ONLY EXPLANATION OF RELIEF OF PAIN:

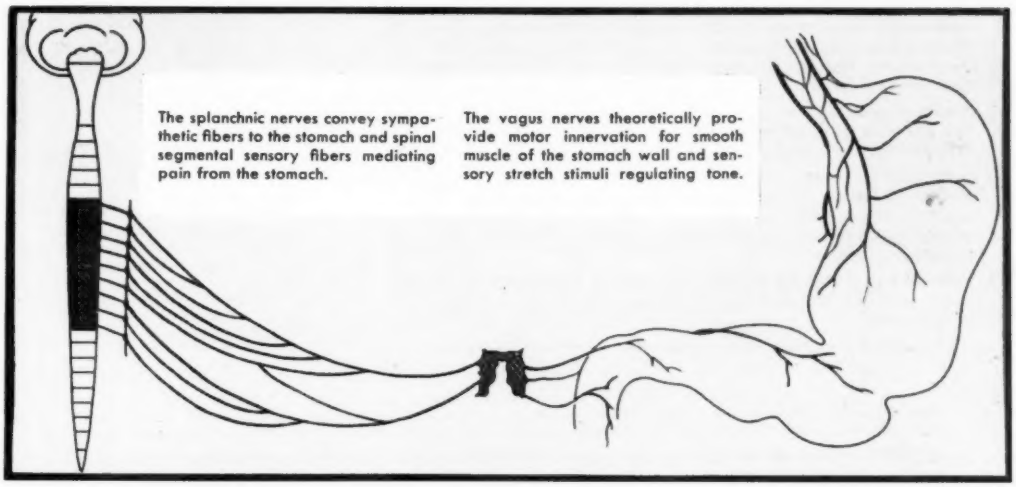
1. 4 patients (B1, C6, D1, & E11) had no free acid before vagotomy but had severe pain.

2. 7 patients (A8, A18, A30, B3, C4, D3, & E9) had little free acid before vagotomy but had severe pain.

3. Introduction into the stomach of 300 cc. of 0.5% HCl produced pain in 11 patients before vagotomy but did not produce pain after operation. 2 of these patients had gastric ulcers and 3 patients had marginal ulcers.

REDUCTION OF MOTILITY AS JUDGED BY BALLOON TESTS OCCURRED IMMEDIATELY AFTER OPERATION IN EACH PATIENT AND HAS PERSISTED WITH THE RELIEF OF PAIN

1. This explanation is based upon consistency of the effect and exclusion of the three possibilities on the left. Nevertheless, restoration of motility by urecholine has failed to reproduce pain and other explanations may exist.

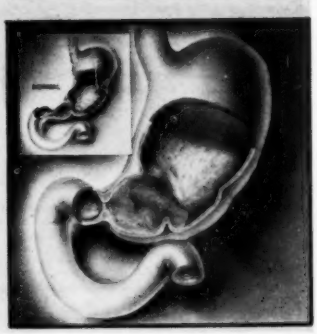

The splanchnic nerves convey sympathetic fibers to the stomach and spinal segmental sensory fibers mediating pain from the stomach.
The vagus nerves theoretically provide motor innervation for smooth muscle of the stomach wall and sensory stretch stimuli regulating tone.

ALTHOUGH EACH OF THE PATIENTS HAS BEEN RELIEVED OF SYMPTOMS OF ULCER AND ABLE TO TAKE AN UNRESTRICTED DIET, RETENTION OR OBSTRUCTION HAS LED TO A VARYING DEGREE OF CLINICAL DIFFICULTY. RETENTION IS PROBABLY CAUSED BY OBSTRUCTION:

OBSTRUCTION MAY BE CAUSED BY CONTRACTION OF SCAR TISSUE AS HEALING OCCURS.

IT MAY ALSO BE AFFECTED BY ABNORMAL CONSTRICTION OF THE PHYSIOLOGICAL PYLORIC SPHINCTER

OR THE SPHINCTER MAY RELAX POORLY BECAUSE OF FAILURE OF PERISTALTIC PROPULSIVE STIMULATIO



OBSTRUCTION PRODUCED 50% OR MORE 6 HOUR RETENTION OF BARIUM IN 22 OF THE 36 PATIENTS WITH DUODENAL OR GASTRIC ULCERS TREATED BY VAGOTOMY ALONE THIS IS STILL PRESENT IN THOSE OBSERVED ONE TO THREE YEARS.

OBSTRUCTION PRODUCED 95 TO 100% RETENTION IN ANOTHER 6 PATIENTS WITH DUODENAL OR GASTRIC ULCER AND NECESSITATED SECONDARY GASTROENTEROSTOMY

CONCLUSIONS

1. Healing or quiescence of duodenal or gastric ulcer has usually followed transthoracic vagotomy and most patients are satisfied with the results. Nevertheless, disturbances of gastrointestinal function including gastric retention have occurred frequently and occasionally produced serious complications. Probably, therefore, vagotomy alone should not be used as a standard treatment for duodenal ulcer
2. Healing or quiescence of stoma ulcer has followed transthoracic vagotomy and since complications caused by retention are less serious, vagotomy may be indicated as standard treatment
3. Transthoracic vagotomy combined with gastroenterostomy has been followed by healing of ulcer and by a low incidence of symptoms of retention. This requires two operations, however, and probably can be accomplished better by subdiaphragmatic vagotomy through a transabdominal approach.
4. Alterations of motor and secretory functions of the stomach have usually persisted as judged by examination made as long as 3 years after vagotomy.

TRANSABDOMINAL VAGOTOMY IS NOW BEING STUDIED AS A TREATMENT FOR DUODENAL ULCER TO DETERMINE WHETHER ITS EFFECTS ARE AS CONSISTENT OR PERMANENT AS THOSE OF TRANSTHORACIC VAGOTOMY A DRAINAGE OPERATION IS ADDED TO AVOID GASTRIC RETENTION.

Transthoracic vagotomy can not be properly evaluated as a treatment of ulcer until patients have been observed over a period of many years and until its effects upon the intestine and other abdominal organs are better known.

CLINICAL COURSE OF 57 PATIENTS TREATED BY VAGOTOMY

GROUPS A, B, C, & D

PATIENT NO.	AGE	DURATION OF SYMPTOMS YEARS	BEFORE VAGOTOMY: ULCER PAIN	HEMORRHAGE	VOMITING	CONSTIPATION	DISABILITY FROM ULCER	INTERVAL MONTHS		AFTER VAGOTOMY: ULCER PAIN	HEMORRHAGE	VOMITING	BOWEL CONSTIPATION	HABIT DIARRHEA	DISABILITY FROM ULCER	DISABILITY OTHER CAUSES	GAIN OR WEIGHT
GROUP A – DUODENAL ULCER								RESULTS									
1	36	14	++++	+	+	+	+++	35	G	0	0	0	0	0	0	0	-6
2	36	6	+++	+	+	+	+++	35	G	0	0	0	0	+T	0	0	+25
3	46	20	++	++	0	+	++	19	G	0	0	0	+	0	0	0	+10
4	29	15	+++	0	+	0	+++	27	G	0	0	0	0	0	0	0	+ 5
5	42	11	++	++++	++	+	++	31	Q	0	0	±	0	+T	0	+++WNCFE	20
6	36	10	+++	+	++	0	+++	20	G	0	0	+	0	+T	0	++PWNCFE	+15
7	63	35	++++	0	+++	+	++	26	Q	0	0	0	0	+	0	CFE	+ 5
8	35	8	++++	+	+++	+	++	27	G	0	0	0	+	+	0	CF	+25
9	38	6	+++	++	++++	0	++	27	G	0	0	+	0	++	0	FE	+ 5
10	44	6	++++	++	++	+	++	26	G	0	0	0	+	0	0	CFE	+29
11	28	4	++++	++	+++	+	++	25	Q	±	0	+	0	+C	0	±DNC	- 3
12	30	7	+++	0	0	+	+++	24	Q	±	0	+	0	+T	0	CFE	+ 3
13	32	6	+	++++	0	0	++	20	G	0	+	0	0	+T	0	E	+ 2
14	31	15	++++	+++	++	+	+++	19 1/2	F	+++	++	+	0	+C	+++	*±NEWC	0
15	52	15	+++	+	+++	0	++	18	G	0	0	+	0	++C	0	DE	+32
16	46	19	+++	+	+	+	++	18	G	0	0	+	+	0	0	±FVC	0
17	51	13	+++	++	+++	+	++	17	G	0	0	+	0	0	0	F	+12
18	27	10	++++	++	++	+	+	15 1/2	G	0	0	+	0	++T	0	C	+13
19	52	20	+++	+	+	+	+++	15	Q	0	0	0	0	+C	0	±WPCFE	6
20	32	5	+++	++	+++	+	++	12 1/2	Q	±	0	0	0	++C	0	++DWC	+14
21	32	1 1/2	+	+++	+	0	+++	12 1/2	G	0	0	0	0	+C	0	CFE	0
22	53	16	++	0	+++	+	++	11	G	0	0	0	+	0	0	CF	5
23	59	10	+++	+++	++	+	++++	11	Q	0	0	0	0	+T	0	**+CFE	3
24	29	9	+++	+	0	+	++	11	Q	0	0	0	0	++C	0	CFE	10
25	40	4	++	+++	+	0	++	10	G	0	0	0	0	+T	0	0	+12
26	42	12	++++	0	0	0	+++	10	S	0	0	0	0	++C	0	***++WFE	-30
27	58	10	++++	0	+++	+	++++	9	G	0	0	0	0	0	0	++WFE	- 7
28	34	4	+++	0	++	+	++	9	G	0	0	0	0	++T	0	E	+16
29	55	1/2	++++	0	+	0	+	9	G	0	0	0	0	+C	0	CF	+15
30	45	3	+++	+	+	+	++	9	G	0	0	0	+	0	0	±WCFE	+ 7
31	30	7	++++	0	+++	0	+++	8	G	0	0	0	+	0	0	±WNFE	+19
32	38	6	++	0	+++	+	++	8	G	0	0	0	0	0	0	0	+10
GROUP B – MARGINAL ULCER AFTER GASTROENTEROSTOMY																	
1	31	3	+++	++	++++	0	+++	25	S	0	0	+++	0	++++C	0	*****++++FPNCVDW	-20
2	35	10	+++	+++	+++	+	++++	34	G	0	0	0	+	0	0	NC	30
3	31	11	++++	0	+	+	+++	8	S	0	0	0	0	+++C	0	±WCEF	+7
GROUP C – MARGINAL AFTER SUBTOTAL GASTRIC RESECTION																	
1	48	7	+++	+++	++	+	+++	27	G	0	0	0	0	+T	0	E	+45
2	64	20	+++	+++	++	+	++	17	S	0	0	+	0	++C	0	+++CDWNE	-15
3	61	16	++++	++++	++	+	++++	15 1/2	G	0	0	0	0	++C	0	+D	+ 8
4	49	12	++++	+++	++++	+	++++	15 1/2	G	0	0	++	0	0	0	CFE	+20
5	41	16	+++	+++	+++	+	+++	11	G	0	0	0	0	0	0	F	10
6	37	11	+++	+	0	0	++	11	G	0	0	0	0	+T	0	0	8
GROUP D – GASTRIC ULCER																	
1	48	3	++++	0	0	+	++	21	G	0	0	0	0	+T	0	C	+13
2	32	5	+++	+	+++	+	+++	12	G	0	0	0	0	0	0	0	+52
3	34	4	+++	0	+	+	+++	12	G	0	0	0	0	++T	0	E	+25
4	28	13	++++	+	++	0	++	11	G	±	0	+	0	++C	0	DCFE	+29

KEY TO CAUSES OF DISABILITY AFTER VAGOTOMY:

G – RESULT CONSIDERED GOOD BY PATIENT (41 PTS.)
F – FAILURE OF HEALING OF ULCER (1 PT.)
Q – RESULT QUESTIONABLE (10 PTS.)
S – COMPLICATIONS OF VAGOTOMY SERIOUS (5 PTS.)

W — WEAKNESS
N — NERVOUSNESS
D — DIARRHEA
V — VOMITING
P — PAIN, CHEST WALL
C — COLICKY ABDOMINAL PAIN
F — FULLNESS OR DISTENTION OF ABDOMEN
E — FOUL ERUCTATION

KEY TO TYPES OF DIARRHEA:

T — TEMPORARY OR PERIODIC DURING FIRST SEVERAL MONTHS AFTER VAGOTOMY.
C — CONTINUOUS SINCE VAGOTOMY.

AFTER VAGOTOMY

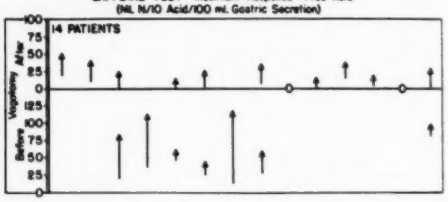
*PERSISTENT ULCER – RESECTION 21 MO.
**DEATH "STROKE" 10 MO.
***MALNUTRITION – PYLOROPLASTY 10 MO.
****DEATH – DIARRHEA & VOMITING 24 MO.

VAGOTOMY ALTERS SECRETIONS OF THE STOMACH OBTAINED BY SUCTION

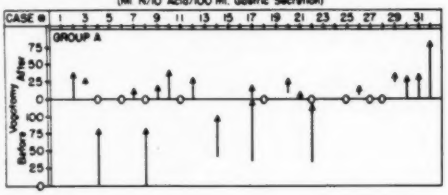
VOLUME OF GASTRIC SECRETIONS ASPIRATED BETWEEN 8:00 P.M. & 8:00 A.M.

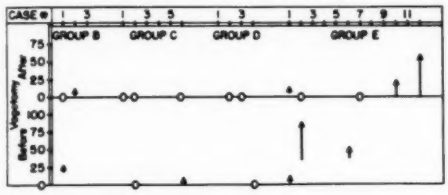
Vagotomy	GROUP A Before	GROUP A After	GROUP B Before	GROUP B After	GROUP C Before	GROUP C After	GROUP D Before	GROUP D After
No. Patients Tested	28	26	2	3	5	6	3	3
Maximum Vol. cc.	2540	1700	1650	600	840	500	650	850
Minimum Vol. cc.	105	20	540	25	185	20	10	5
AVERAGE cc.	919	337	1020	352	528	196	553	409

CAFFEINE TEST – Maximum Response – Free Acid (Ml. N/10 Acid/100 ml. Gastric Secretion)

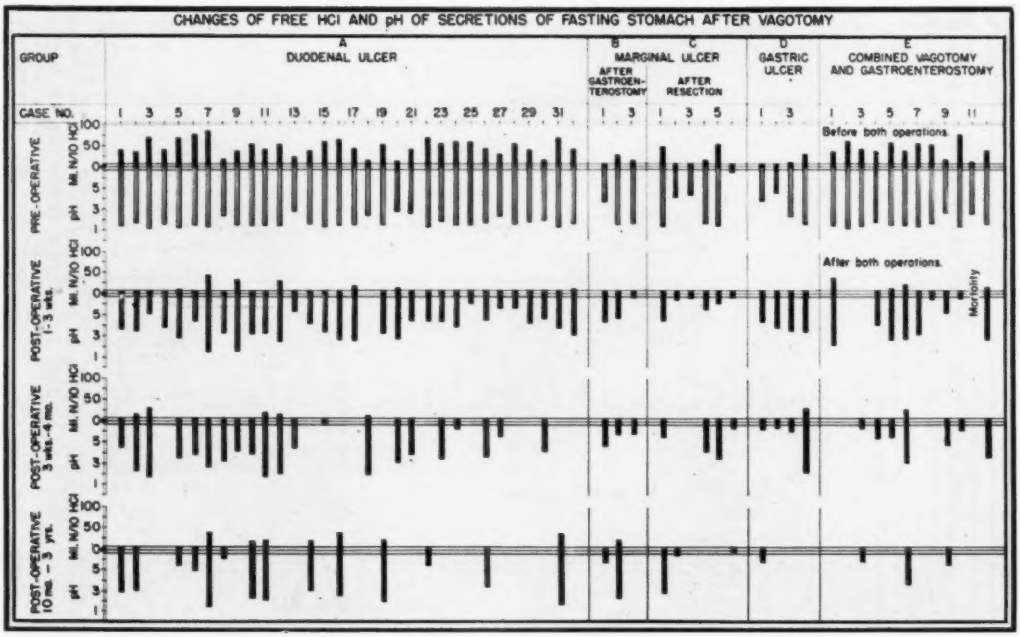


INSULIN TEST – Maximum Response – Free Acid – 1 week to 4 months (Ml. N/10 Acid/100 ml. Gastric Secretion)





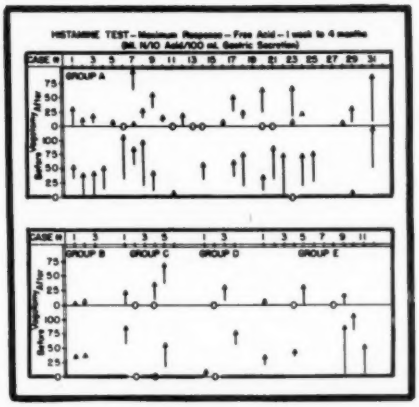
CHANGES OF FREE HCl AND pH OF SECRETIONS OF FASTING STOMACH AFTER VAGOTOMY



VAGOTOMY HAS BEEN COMBINED WITH GASTROENTEROSTOMY IN 12 OF THE 57 PATIENTS

BEFORE COMBINED VAGOTOMY & GASTROENTEROSTOMY

PATIENT NO.	AGE	LOCATION OF ULCER	DURATION OF SYMPTOMS YEARS	ULCER PAIN	HEMORRHAGE	VOMITING	CONSTIPATION	DISABILITY FROM ULCER
GASTROENTEROSTOMY WAS CONSIDERED NECESSARY AFTER VAGOTOMY IN 5 PATIENTS								
1	41	Stoma	8	+++	0	+	+	++++
2	41	Duodenum	3	++	++++	+	+	+++
3	29	Duodenum	10	+++	0	+++	0	+++
4	58	Duodenum	12	++++	0	+++	+	+++
5	52	Antrum	5	++++	++	+++	0	+++
GASTROENTEROSTOMY WAS CONSIDERED ADVISABLE AT TIME OF VAGOTOMY IN 5 PATIENTS								
6	46	Duodenum	10	+++	0	+	+	++
7	34	Antrum	8	++++	0	0	+	+++
8	63	Duodenum	10	++++	0	+++	+	++++
9	43	Duodenum	20	+++	+	+++	+	+++
10	55	Duodenum	30	++++	++	+++	+	++++
GASTROENTEROSTOMY WAS PERFORMED BEFORE VAGOTOMY IN 2 PATIENTS								
11	53	Antrum	23	+++	0	0	0	++
12	49	Duodenum	28	+++	++++	++++	0	++++



GROUP E

AFTER COMBINED VAGOTOMY & GASTROENTEROSTOMY

TYPE OF GASTROENTEROSTOMY	INTERVAL BETWEEN OPERATIONS	INTERVAL AFTER OPERATIONS	ULCER PAIN		HEMORRHAGE	VOMITING	BOWEL HABIT CONSTIPATION	BOWEL HABIT DIARRHEA	DISABILITY FROM ULCER	DISABILITY OTHER CAUSES	GAIN OF WEIGHT
RESULTS											
Pyloroplasty	105 days	27 mos.	G	0	0	0	0	0	0	++ WNGFE	-6
Jejunostomy	26 days	26 mos.	Q	±	0	0	0	+C	0	0	+35
Pyloroplasty	11 days	20½ mos.	G	0	0	0	+C	+C	0	0	30
Pyloroplasty	14 days	17 mos.	G	0	0	0	0	0	0	0	+26
Pyloroplasty	29 days	8 mos.	Q	±	+	0	0	0	0	WNG	0
Jejunostomy	0 days	18 mos.	G	0	0	0	0	++T	0	0	25
Pyloroplasty	0 days	13½ mos.	G	0	0	0	0	++T	0	0	36
Pyloroplasty	0 days	11 mos.	G	0	0	0	0	0	0	0	-2
Exclusion	0 days	10½ mos.	G	0	0	0	0	+C	0	0	+10
Pyloroplasty	0 days	23 days	S		Mortality						
Pyloroplasty	63 days	10½ mos.	G	0	0	0	0	+T	0	+WPE	0
Exclusion	33 days	10 mos.	G	0	0	0	0	0	0	+W	-7

Bacteriologic, Etiologic, and Serologic Studies in Epilepsy and Schizophrenia II.

EFFECTS IN ANIMALS FOLLOWING INOCULATION OF ALPHA STREPTOCOCCI

EDWARD C. ROSENOW

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THE occurrence of convulsions and of psychotic symptoms in low incidence during various infective diseases, some due to neurotropic viruses as now understood, has been considered as presumptive evidence in favor of an infectious etiology of epilepsy and schizophrenia.[15] The possibility that specific types of streptococci might in some way be causative was suggested in experiments on elective localization and specificity of alpha streptococci as isolated in studies of diseases of the nervous system.

Streptococci isolated from patients with infectious peripheral neuritis, when given intravenously to rabbits localized and produced lesions in the peripheral nerves.[1, 2] The streptococci isolated in studies of herpes zoster, a disease now considered to be due to a virus, localized and produced lesions in the posterior columns of the spinal cord and intervertebral ganglia associated with blistering of the skin and great pain characteristic of that disease.[3]

The streptococci isolated in studies of intercostal neuralgia localized in posterior roots of intercostal nerves of rabbits on intravenous injection.[4] The streptococci freshly isolated from a dying pulp of a tooth and from an excised piece of inflamed muscle in a patient suffering from a recurrent severe attack of dental neuritis and myositis localized electively in the pulps of teeth, the dental nerves, and muscles of rabbits and dogs following intravenous injection.[5]

Spasms of the diaphragm were produced consistently on intracerebral inoculation of living cultures, the heat-killed streptococci, and filtrates of active cultures of the streptococcus as isolated in studies of epidemic and persistent postoperative hiccup.[6] Postoperative "ether convulsions" have been reproduced experimentally with a specific type of neurotropic streptococcus.[7] Alpha streptococci freshly isolated from nasopharynx, stool, spinal fluid, and the virus of poliomyelitis on appropriate injection produced flaccid paralysis in guinea pigs, rabbits, and monkeys as the outstanding manifestation,[8] whereas the streptococci similarly isolated in studies of encephalitis[9, 10] produced the symptoms of encephalitis often corresponding in type to the encephalitis in the patient from whom the streptococci was isolated.[11]

The symptoms and lesions characteristic of Sydenham's chorea were produced in rabbits on intracerebral and intravenous injection of the streptococcus isolated from the nasopharynx of patients suffering from Sydenham's chorea, and were produced in dogs through the induction of chronic foci in the teeth with the streptococcus.[12] Spasmodic

This is second of a series of three papers by Dr. Rosenow in which are recorded the results of bacteriologic and experimental studies on the etiology of epilepsy and schizophrenia. The third paper will appear in a later issue of *Postgraduate Medicine*.

torticollis was produced in high incidence in rabbits,[13] and the strange syndrome of respiratory arrhythmia and mental deterioration following encephalitis was closely simulated[14] on intracerebral injection of the streptococci isolated from the nasopharynx of respective patients.

It should be emphasized that these highly specific results were obtained by the use of special methods. The usual methods did not suffice.[15] Other workers who have used methods essentially like those we have used have reported similar highly specific results in a wide range of diseases, involving tissues derived from both mesoderm and ectoderm. Numerous reports by different investigators deal especially with the question of specificity of alpha streptococci in the causation of disease.*

The concept has been set forth that highly specific types of streptococci may be causative in epilepsy and schizophrenia; for this concept to be valid, proof is needed to show that such specificities may be acquired and that perhaps hereditary predisposition may provide the very conditions favorable for streptococci to acquire the respective specific properties. Experimental evidence is not lacking to show that changes in specificity of alpha streptococci do occur in response to changes in environment. The continual presence of neurotropic and arthrotropic alpha streptococci, respectively, in patients having "neuropathic" or "arthropathic" hereditary predispositions and suffering from chronic encephalitis and chronic arthritis, respectively, has been shown.[31]

Changes in vitro from one type of specificity of alpha streptococci into other types often characteristic of those at hand in, or the cause of, epidemic diseases have been shown to occur seasonally,[32] and have been induced by growth on certain artificial mediums,[1] by successive passage through animals,[33] and by exposing cultures to a high-frequency field of radiant energy.[34] Changes in localization of the freshly isolated streptococci in rabbits following intravenous injection matched changes in localization which occurred spontaneously in patients during successive outbreaks of epidemic hiccup and of neuromyeloencephalitis.[35] The importance of the principles of microbic dissociation in the causation of disease in accord with these experiments has been especially emphasized by Hadley.[36]

EDWARD C. ROSENOW

LOCALIZATION in animals on injection of living cultures of streptococci, the heat-killed organisms, and the toxic components in filtrates of cultures in my studies were often so precise as to resemble the specific pharmacologic action of drugs and chemicals.[37]

Streptococci isolated from the nasopharynx and infected pulpless teeth of persons suffering from epilepsy and schizophrenia have been shown to possess neurotropic distribution curves of cataphoretic velocity.[38] A number of persons who were in the early stages of epilepsy and of psychoneurosis recovered following therapeutic injections of autogenous vaccines prepared from streptococci with neurotropic cataphoretic velocity[38] and one which had produced spasms or mental disorientation, respectively, in rabbits on intracerebral injection.

*Haden,[16] Barnes and Giordano,[17] Nickel and Hufford,[18] Cooper,[19] Harly and Brinch,[20] Welsh,[21, 22] Meisser and Gardner,[23] Cook,[24] Bernhardt,[25] Irons, Brown, and Nadler,[26] Kelly,[27] Topley and Weir,[28] Wilkie,[29] and Jones and Newsom.[30]

It is the purpose of this paper to describe the methods used, to record unpublished experiments on Macaccus rhesus monkeys which had been inoculated with streptococci from diverse sources, and to report results obtained in a bacteriologic study of epilepsy and schizophrenia and of the localization in animals of the respective streptococci as isolated.

METHODS

Nasopharyngeal swabbings of patients suffering from various diseases, including epilepsy and schizophrenia, were made with aluminum-wire-wrapped swabs bent to a suitable angle so as not to touch the tongue. Pus from tonsils was expressed and scooped with a small bent laryngeal mirror. Purulent material from the depth of pyorrhea pockets was aspirated into capillary pipettes. Severed apexes of pulpless teeth were extracted in a sterile manner. Each of these materials was suspended in 2 ml. of a 0.2 per cent gelatin-Locke or isotonic sodium chloride solution for cultures, precipitation tests, and inoculation of animals.

Cultures were made from spinal fluid, from the centrifugated sediment of freshly voided urine, and from suspensions of stool in sodium chloride solution. The surface of horse blood agar plates was inoculated routinely, and serial dilution cultures[39] were made in mediums affording a gradient of oxygen tension, usually alternately in dextrose-brain broth (0.2 per cent dextrose) and soft dextrose-brain agar (0.2 per cent dextrose and 0.2 per cent agar) in tall (12 cm.) columns in test tubes (⅝ x 6 or 8 inches). The dextrose-brain broth and dextrose-brain agar were usually freshly prepared by adding before autoclaving approximately 1 part by volume of pieces of fresh or frozen calf or young beef brain to approximately 7 volumes, or 15 ml., of the medium, previously adjusted to *p*H 7.2 and then autoclaved at 15 pounds pressure for twenty minutes.

The amount of inoculum in the first tube and the degree of serial dilution was determined roughly by the number and kind of organisms found in Gram-safranine stained films of the material under study. Serial, one hundredfold, dilutions or 10^{-2} of the materials suspended in sodium chloride solution were usually made by transferring 0.15 ml. from tube to tube with a 1 ml. pipette, and 10,000 fold or 10^{-4} dilutions of cultures were made by transferring 1.5 ml. from tube to tube with nichrome wire. The same pipette or wire was used for the serial dilutions without sterilizing between transfers. Hence, the successive dilutions represent dilutions of liquid and not necessarily corresponding dilutions of organisms.

Seven ml. of blood were routinely drawn from the vein at the bend of the elbow into sterile vacuum tubes. The blood was allowed to clot. The rubber stopper was then removed, in a sterile manner, the clot loosened with a sterile capillary pipette, the rubber stopper replaced, and the vial centrifuged. The serum was decanted then, and in a sterile manner, the partially macerated clot was transferred into 200 ml. of freshly prepared dextrose-brain broth. The small amount of blood remaining in the stoppered vial and the inoculated dextrose-brain broth were then incubated. Gramsafranine stained films were made and examined for bacteria as soon as evidence of growth in the broth had occurred, and in five or seven days such films were made from the blood residue in the vial and from the sediment of seemingly negative cultures. All cultures were incubated at 33°C. to 35°C.

Pure cultures of the streptococci for inoculation of animals and other studies were obtained not from primary blood agar plates, but from the end point of growth of usually young primary serial dilution cultures alternately in dextrose-brain broth and dextrose-brain (agar or from young primary cultures in dextrose-brain) broth. Blood agar plates were made of these to determine the type of streptococcus and to check the purity of the cultures.

Monkeys were inoculated intracerebrally usually with 1.5 ml. of the washings of nasopharyngeal swabbings of patients, of corresponding pure cultures in dextrose-brain broth or autoclaved chick embryo medium of the streptococci diluted 1:200 or more, and of emulsions or filtrates of emulsions of the brains and spinal cords of mice, rabbits, or monkeys that had succumbed to poliomyelitis, polio-encephalitis, or encephalitis following intracerebral inoculation. In some instances intraspinus, intravenous, and intramuscular inoculations were given in addition to intracerebral inoculations.

Inoculations were repeated at short or long intervals as indicated by the absence, character, and duration of symptoms and by the nature of the inocula.

Rabbits and mice were inoculated either directly with suspensions in saline or with material obtained from nasopharynx, tonsils, or teeth; with the primary cultures in dextrose-brain broth, with suspensions of single colonies likewise from the end point of growth, or with dextrose-brain broth cultures of freshly isolated strains after a variable number of rapidly repeated subcultures in dextrose-brain broth. Intracerebral inoculations in all instances were made under ether anesthesia.

Routinely, two rabbits were inoculated intracerebrally, one with 0.1 ml., the other with 0.2 ml., of the saline suspensions or with like amounts of 1:200 to 1:10,000, or greater dilution, of the pure cultures of the streptococci in dextrose-brain broth. Mice at first were inoculated intracerebrally with 0.03 ml. of the suspensions and of 1:10 dilution of the pure cultures and intraperitoneally with 1.2 ml. of undiluted cultures. After it was found that largely negative results were obtained as regards the occurrence of characteristic symptoms, a larger number of streptococci was inoculated. Accordingly 0.03 ml. of 10:1 suspensions in sodium chloride solution of young dextrose-brain broth cultures, 20:1 suspensions of the heat-killed organisms, and 10 per cent emulsions of the brains of mice that had succumbed were inoculated intracerebrally, and 0.1 ml. of 20:1 suspensions of dextrose-brain broth cultures of the streptococci were inoculated intranasally. Filtrates of dextrose-brain broth cultures were injected intracerebrally and intravenously in sodium chloride solution in 0.03 ml. and 1 ml. amounts, respectively.

The animals were observed and symptoms recorded at frequent intervals during the day and at crucial points several times during the night. They were examined for lesions under a strong light as soon after death as possible, and cultures were made on blood agar plates and into dextrose-brain broth of brain substance admixed with

cerebrospinal fluid and from the blood from the heart. Pieces of the brain were placed in 10 per cent formalin for sections.

RESULTS OF CULTURES

Cultures on blood agar plates were made of nasopharyngeal swabbings from 181 persons suffering from epilepsy, from 258 persons suffering from schizophrenia, from 85 persons suffering from chronic or subacute arthritis, and as a control from 78 well persons. Green-producing colonies of alpha streptococci grew in predominating numbers in most instances and indifferent colonies grew in a few. Hemolytic or beta streptococci grew in a small number of instances and were never present in predominating numbers. Variable numbers of colonies of Micrococcus catarrhalis and staphylococci grew in most instances, and in no instance did Hemophilus influenzae grow in large numbers. There was no distinctive difference between the type of colonies that grew in the different groups. In general, however, the number of colonies was greater, often far greater, in the cultures from persons who were ill than was observed in comparable cultures from well persons.

Shake cultures in blood agar and serial dilution cultures in dextrose-brain broth or alternately in dextrose-brain broth and dextrose-brain agar were made from the spinal fluid in 24, from the urine in 10, from the apexes of pulpless teeth extracted in a sterile manner in 24, and from the stool in 23 persons suffering from schizophrenia. The spinal fluids proved sterile; greening streptococci were isolated in small numbers from the urine and in large numbers from the teeth; and greening or indifferent streptococci were isolated in 19 of the 23 stools cultured.

Cultures in the dextrose-brain broth of the partially macerated blood clot yielded highly pleomorphic greening or indifferent streptococci to blood agar in 49, or 29 per cent, of 161 persons suffering from epilepsy, in only 5, or 4 per cent, of 125 persons suffering from schizophrenia, and in 7, or 14 per cent, of 69 persons having chronic arthritis; the cultures from 62 well persons or persons suffering from noninfectious ailments yielded nothing. The incidence of isolation of streptococci from the blood in persons having epilepsy was highest shortly before or during seizures, and most of the 49 persons from whose blood the streptococcus was isolated were taking phenobarbital or dilantin or both at the time the blood was drawn.

Agglutination tests were made with antiserums prepared in horses and rabbits and with thermal antibodies prepared in vitro with streptococci isolated from nasopharynx or blood in studies of epilepsy, schizophrenia, and arthritis and with the respective serums on the streptococci isolated from the nasopharynx, teeth, blood, urine, and stool. Results of these studies and of the precipitation and intradermal tests with the respective antiserums and thermal antibodies will be reported elsewhere. Suffice it to state here that evidence of respective specificity of the streptococci isolated from the nasopharynx, teeth, and blood was obtained by each of these methods, whereas the strains of streptococci isolated from urine and stool proved nonspecific.

RESULTS OF EXPERIMENTS IN MONKEYS

Convulsions and disorientation of mental processes sometimes occur during or following streptococcal or other infections. In order to determine the conditions under which streptococci and other causative agents may cause spasms or convulsions and disorientation, we reviewed the results of a large number of experiments in monkeys in which such symptoms sometime developed following inoculation of (1) natural or experimentally produced poliomyelitic and encephalitic virus, (2) of streptococci isolated from these and from nasopharynx and spinal fluid of patients and monkeys that had succumbed to poliomyelitis, polioencephalitis, or encephalitis, and (3) of streptococci isolated from nature in relation to epidemics of poliomyelitis and encephalitis and in relation to nonepidemic diseases.

Of a total of 1,338 monkeys that were inoculated with cultures of streptococci or material containing streptococci during the years 1917 to 1944, spasms or convulsions were recorded to have occurred in 109, or 8 per cent, and symptoms simulating in certain respects those of schizophrenia in 24, or 1.8 per cent. Table 1 summarizes the incidence of spasms or convulsions that developed in the Macaccus monkeys following inoculation of material containing streptococci in relation to poliomyelitis and encephalitis and the incidence of the demonstration in, or the isolation of, streptococci from spinal fluid or brain of animals in which spasms developed.*

It will be seen that the incidence of spasms or convulsions and the demonstration of streptococci in spinal fluid or brain in the monkeys in which spasms had developed, in general, paralleled the incidence of spasms or convulsions and the ease with which streptococci are demonstrable in the respective spontaneous diseases. Moreover, the incidence, severity, and duration of spasms of convulsions in the different groups of inoculated monkeys paralleled roughly the incidence of spasms which occur in spontaneous poliomyelitis, polioencephalitis, and encephalitis.

The drop in incidence of spasms from 26, or 54 per cent, of the 48 monkeys that received the experimental streptococcal virus while in the encephalitic phase to 3, or 6 per cent, of 51 monkeys that received the experimental virus in the poliomyelitic phase is especially noteworthy.[40, 41, 42] Of 109 monkeys developing spasms, 36 of them received Berkefeld or Seitz filtrates of brain or cord emulsions of animals that had been inoculated with virus containing streptococci or with filtrates of chick embryo cultures of streptococci; 48 received emulsions of the brains of mice, rabbits, or monkeys that had been inoculated with natural or experimentally produced virus and from which streptococci were isolated; and 25 received cultures of neurotropic alpha streptococci in high dilution.

The onset of spasms ranged from two to sixteen days after inoculation in the different groups and averaged 5.2 days. In most instances the spasms resembled those obtained following inoculation of the streptococcus isolated

*The experiments on monkeys and on some of the rabbits were done at the Mayo Foundation for Medical Education and Research, Rochester, Minnesota, during the course of studies on the relation of the streptococcus to poliomyelitis and encephalitis and their respective viruses.

TABLE 1

INCIDENCE OF SPASMS OR CONVULSIONS IN MACACCUS RHESUS MONKEYS FOLLOWING INOCULATION OF NATURAL AND EXPERIMENTAL POLIOMYELITIC AND ENCEPHALITIC VIRUS AND OF NEUROTROPIC ALPHA STREPTOCOCCI ISOLATED IN STUDIES OF POLIOMYELITIS AND ENCEPHALITIS

MATERIAL INOCULATED		STRAINS	MONKEYS					
			INOCULATED	IN WHICH SPASMS OR CONVULSIONS DEVELOPED:		AND IN WHICH THE STREPTOCOCCUS WAS DEMONSTRATED IN SPINAL FLUID OR BRAIN:		
				NUMBER	PER CENT	NUMBER EXAMINED	YIELDING STREPTOCOCCI	
							NUMBER	PER CENT
Natural poliomyelitic virus		12	214	17	8	12	5	42
Natural encephalitic virus		17	97	18	19	13	8	62
Experimental streptococcal virus in:	Encephalitic phase	6	48	26	54	22	12	55
	Poliomyelitic phase	6	51	3	6	3	1	33
Alpha streptococci isolated from nasopharynx, spinal fluid, or brain and spinal cord of persons and monkeys that had poliomyelitis or encephalitis		23	162	25	15	20	15	75
Alpha streptococci isolated from milk and water supplies, from air, flies, and bedbugs (Cemex lectularius) in relation to poliomyelitis and encephalitis		20	57	20	35	13	9	69
Total		80	629	109	17	83	50	60

in studies of myoclonic encephalitis.[11] In a few instances the character of the spasms resembled petit mal and grand mal of epilepsy, well illustrated in Protocol 1 later in this paper. The results obtained in monkeys inoculated with the streptococcus isolated in studies of epilepsy are depicted in Protocol 2.

The strange behavior, such as the threatening to attack, the extreme excitation in which the animal dashed about violently, the apparent seeing of imaginary objects or hearing of noises, and cataleptic states, occurred as an integral part of other symptoms, such as blurred vision or blindness, nystagmus, myoclonic spasms, and flaccid or spastic paresis or paralysis (Protocol 3). Aside from a variable congestion of the brain of the monkeys in which spasms or disorientation had developed, little was found at necropsy. Abscess and grossly visible meningitis were absent. Microscopic sections in general revealed the lesions characteristic of the respective experimental disease in question.

During the course of these studies, I had opportunity to inoculate monkeys and rabbits with streptococci isolated from the nasopharynx of a patient, a middle-aged woman, who was suffering from an acute attack of "psychoneurosis." The patient made a slow recovery under insulin shock treatment. She remained apparently well for eight years, when she had a recurrence incident to the death of a son.

My studies were made at the time of an attempted suicide during her first attack. Material obtained on the swab from her nasopharynx was washed off in 2 ml. of the sodium chloride solution. Blood agar streak cultures of the sodium chloride suspension revealed large numbers of colonies of alpha streptococci, and short-chained streptococci grew out in pure culture in dextrose-brain broth. The sodium chloride solution suspension of the nasopharyngeal swabbing was inoculated intracerebrally into the right frontal lobe of two rabbits and one monkey.

Severe tremors and excitation developed in both rabbits. At times they dashed about in a wild fashion unmolested in their cages. Hemorrhagic edema of the lungs and severe congestion of the brain were found at necropsy in both rabbits, and large numbers of the streptococci were isolated from the brain and blood after death.

SYMPTOMS in the monkey were similar. It became extremely excitable the day after inoculation. On the second day, and for five days thereafter, excitability and hyperirritability were extreme. The animal seemed disoriented most of the time. It often acted as if it saw imaginary threatening objects always on its left side. Spinal puncture made on the day following inoculation revealed slightly turbid fluid from which the streptococcus was isolated in pure culture. The brain after death was diffusely congested. There was no gross evidence of meningitis and no mark at the site of intracerebral inoculation in the right frontal lobe. A large blood clot was found in the left cerebral ventricle adherent to the choroid plexus. The viscera were normal. Cultures in dextrose-brain broth of pipettings of the brain substance admixed with cerebrospinal fluid yielded a pure culture of the streptococcus. Cultures from the blood and brain on blood agar plates proved sterile.

One additional rabbit was inoculated with 1.2 ml. of a 1:200 dilution of the dextrose-brain broth culture of the streptococcus isolated from the spinal fluid on the

second day, and one monkey was given 2 ml. intracerebrally and 3 ml. intraspinously of a Berkefeld filtrate of 10 per cent emulsion of the brain of the monkey. The third rabbit developed symptoms similar to those shown by the two rabbits that received the sodium chloride solution suspension from the nasopharynx of the patient. The monkey remained free from symptoms for twenty days, when it became extremely excitable and repeatedly threatened to charge when observed unmolested in its cage. On being prodded it developed severe tremors and slight clonic spasms. The temperature was 106°F. The following day the temperature was 105.2°F. It continued to be extremely excitable, threatening to charge for several days; then it recovered gradually. It remained well for three months, when it was inoculated with material from another source.

EXPERIMENTS IN RABBITS WITH STREPTOCOCCI ISOLATED IN STUDIES OF EPILEPSY AND SCHIZOPHRENIA

The occurrence at times of spasms or convulsions and of disorientation in monkeys following inoculation of streptococci or material containing streptococci from diverse sources led to a study of the effects in rabbits of streptococci isolated in studies of epilepsy and schizophrenia. The results obtained in rabbits are summarized in Table 2. When rabbits were inoculated with the living cultures of the streptococcus, the dead bacteria, and filtrates of cultures from the nasopharynx and blood of persons suffering from epilepsy, the incidence of hyperirritability was far less, the incidence of tremors was about the same, and the incidence of spasms and convulsions was far greater than when they were given identical inoculations of the streptococcus isolated from the nasopharynx of persons suffering from schizophrenia. The mortality and isolations of streptococci from the brains of rabbits that succumbed was about the same in the two groups, but the isolations of streptococci from the blood following inoculation of the streptococcus from epilepsy was from three to five times as great in the different groups that received living streptococci as following inoculation of the streptococcus from schizophrenia.

The source and type of inocula, the number and type of streptococci, and the time of onset of symptoms were all comparable. But as symptoms progressed, a striking difference became apparent. Severe tremors and spasms of masseters, generalized tremors and ataxia, clonic and tonic spasms, and often recurring generalized convulsions resembling grand mal developed in rabbits that received the living or dead streptococci or the filtrate of cultures isolated from the nasopharynx or blood of persons suffering from epilepsy (Protocols 4 and 5). In sharp contrast extreme hyperirritability with evidence of disorientation usually without spasms developed in the rabbits inoculated with the streptococcus isolated from the nasopharynx of persons suffering from schizophrenia or manic-depressive psychosis (Protocol 6).

Symptoms characteristic of the disease in question usually developed in a large percentage of animals inoculated with the streptococcus of a given case, especially if cultures were obtained at the time of acute attacks. Myoclonic spasms developed in each of a group of rabbits inoculated respectively with the streptococcus isolated from the nasopharynx, blood, and an extracted pulpless tooth of a man, a teacher who was becoming incapacitated because of recurring attacks of grand mal. Following the extraction of the tooth, his attacks of grand mal disappeared and had not recurred for nine years.

In sharp contrast, severe tremors and extreme hyperirritability sometimes accompanied by mild clonic spasms developed in each of 11 rabbits following intracerebral inoculation of a highly diluted culture of the streptococcus isolated, shortly after death, from the nasopharynx of a young woman who committed suicide by jumping from the top of a tall building during an acute attack of "psychoneurosis." The streptococcus inoculated was so far removed from the original source as to eliminate the possibility of the presence of virus.

RESULTS OF EXPERIMENTS IN MICE

At first mice were inoculated intracerebrally with 0.03 ml. of the sodium chloride solution suspension or with the primary young culture of the streptococcus undiluted or diluted 1:10 in sodium chloride solution of nasopharyngeal swabbings of persons suffering from epilepsy or schizophrenia. The results were considered as suggestive of specificity of the respective streptococci.

Thus, 8, or 18 per cent, of 43 mice that received the streptococcus from 35 persons suffering from epilepsy were seen to have severe tremors, twitchings, and mild clonic spasms, and 68, or 33 per cent, of 205 mice similarly inoculated with the streptococcus from the nasopharynx of 55 persons who were suffering from schizophrenia developed hyperirritability and, more rarely, catatonic states that were usually without spasms.

Since mice proved relatively resistant to the streptococcus, it was thought that if larger numbers of the streptococci were inoculated, especially streptococci obtained from the end point of growth in serial dilution cultures of dextrose-brain broth, a higher incidence of respective specific effects might be obtained. Accordingly, we inoculated intracerebrally 0.03 ml. of 10:1 suspensions in saline of dextrose-brain broth cultures and suspensions of similar density of the streptococci from streak cultures on blood agar plates made with the brains of mice that succumbed to inoculations.

In the experiments summarized in Table 3, two pooled suspensions of streptococci from cultures at the end point of growth of the nasopharyngeal swabbings—one from 13 and the other from 11 persons suffering from severe epilepsy—and corresponding cultures from each of 5 other persons having epilepsy, or seven suspensions in all, were inoculated into 17 mice in the first animal passage; 4 strains were used in the second passage; and then further animal passages were made with the strain derived from pooled cultures from the 11 cases. Spasms occurred in the mice following the inoculation of each of the suspensions of the different pools and strains. The cultures from the nasopharynx of well persons used as a control group were similarly pooled and similarly inoculated. Spasms developed in only 3 of 23 mice in the first passage, and in none of 21 mice in the second passage; hence, no further animal passage of control strains were done.

It will be seen that the incidence of spasms and convulsions following intracerebral inoculation of the living

TABLE 2

MORTALITY, SYMPTOMS AND SIGNS, AND ISOLATION OF STREPTOCOCCI FROM THE BRAIN AND BLOOD OF RABBITS FOLLOWING INTRACEREBRAL INOCULATION OF STREPTOCOCCI ISOLATED FROM PERSONS SUFFERING FROM EPILEPSY AND SCHIZOPHRENIA

Source of streptococci	Material injected intracerebrally	Strains or cases	Rabbits		Symptoms or findings in per cent				Streptococci			
									Brain		Blood	
			Injected	Per cent died	Hyperirritability	Tremors	Spasms	Convulsions	Cultured	Per cent	Cultured	Per cent
Epilepsy (46 Cases)	Suspension of material directly from nasopharynx, tonsils, or teeth	37	72	65	29	**75**	**75**	**33**	47	94	46	26
	Dextrose-brain broth cultures from nasopharynx, tonsils, teeth, or blood diluted 1:200 to 1:10,000	26	34	91	15	**74**	**73**	**35**	25	92	23	43
	Total for material containing living streptococci	63	106	74	25	**75**	**75**	**34**	72	93	69	32
	Heat killed streptococci and filtrates of dextrose-brain broth cultures	10	19	58	11	**74**	**79**	**47**	11	0	6	0
Schizophrenia (45 Cases)	Suspensions of material directly from nasopharynx or dextrose-brain broth cultures diluted 1:200 to 1:10,000	45	77	87	**87**	**79**	21	3	54	83	46	7

streptococcus obtained from persons suffering from epilepsy was remarkably high throughout nine successive passages, averaging 93 per cent and 69 per cent, respectively, and that spasms and convulsions almost never occurred in control mice inoculated in identical manner with the streptococcus isolated from the control group of well persons. The incidence of spasms and convulsions following inoculation of suspensions of the heat-killed streptococci and filtrates of dextrose-brain broth cultures of streptococci isolated from persons having epilepsy was also high, whereas no spasms developed in mice that received suspensions and filtrates from the control group.

The statistical evidence of specificity shown in Table 3, though striking, does not express adequately the specific character and type of symptoms that developed in these mice following inoculation of the living and the heat-killed streptococcus and filtrates of cultures.

The mice usually remained apparently well for from four to twelve, and sometimes for twenty-four, hours after inoculation. Evidence of illness was first manifested by their becoming abnormally quiet and standing humped up with roughened fur and by increased respiration and fine and coarse tremors; these were followed somewhat later by hyperirritability, and then in rapid succession by scratching of the nose or side of the head, severe tremors, twitching, and clonic spasms of muscles of the face, ears, neck, and extremities. They then fell to the side as the head was pulled violently to one side or other or backward, as generalized tonic followed by clonic spasms and often voiding of urine occurred. These symptoms were followed in turn by increased respiration as they lay relaxed, apparently unconscious and insensitive for a moment to stimuli or proddings. Recovery often appeared to be complete as symptoms developed soon after inoculation, but as symptoms became worse hour by hour or day by day, the spasms and convulsions were almost continuous, and in most instances the mice died apparently from exhaustion during seizures resembling "status epilepticus."

Of the 130 mice inoculated with the streptococcus from the nasopharynx of persons suffering from severe epilepsy, 102, or 78 per cent, died in from one to eight days. Spasms did not occur at all in 12 of the 28 that survived, and the recurring seizures in the remaining 16 disappeared during the course of two weeks.

Of the 44 mice inoculated with the streptococcus from the nasopharynx of well persons used as a control, 12, or 27 per cent, died. Seven of these died within twenty-four hours, and 5 died on the second day after inoculation.

The tendency of the strains from persons having epilepsy to produce spasms and convulsions when grown in dextrose-brain broth persisted through consecutive serial dilution cultures representing dilutions of original inoculum of at least 10^{-10} to 10^{-80}, and as shown in Table 3, persisted through nine consecutive passages through mice following inoculation of brain emulsions, primary cultures, and of from three to five subcultures rapidly repeated. The spasm-producing property was found to be present in undiminished form in one strain that had been passed through six series of mice on isolation after it was kept at room temperature dried on glass balls in vacuo under a dessicant and on a sealed blood agar slant for three weeks and after seven rapidly repeated (two or three per day) subcultures in dextrose-brain broth. It was

then subcultured in dextrose-brain broth every third or fourth day for five additional subcultures, whereupon it had not only lost the power to produce spasms but apparently all virulence, since spasms did not develop in any of the 10 mice, 2 rabbits, and 2 rats inoculated, and all animals survived.

Having found a fairly precise method for measuring symptom-producing and localizing power of streptococci in mice, we studied the comparative effect on mice of the intracerebral and intranasal inoculation of streptococci isolated from the nasopharynx of persons suffering from different types of epilepsy, persons suffering from dementia paralytica with and without convulsions, of well persons; and also the inoculation of streptococci isolated from the brain of an uninoculated baby mouse that died in convulsions, and of streptococci isolated from poliomyelitic virus virulent for monkey and mice.*

The mother of the baby mouse that was seen to die in spasms had been inoculated intranasally several times, in the early stages of gestation, with the streptococcus from a person suffering from grand mal epilepsy in the seventh mouse passage. No symptoms were noted either in the mother mouse or in the three litter mates which grew to maturity without spasms or convulsions.

The streptococci from the end point of growth of the usual serial dilution cultures were inoculated intracerebrally under ether anesthesia in the usual and comparable dosage for the different strains. Intranasal inoculations were made under deep ether anesthesia with 20:1 suspensions in sodium chloride solution of the respective streptococci. These were usually repeated once or twice daily for three or four times. An attempt was made to lower the inherently high resistance of the brain to invasion of noxious agents, by injecting 0.03 ml. of sterile sodium chloride solution intracerebrally just before or after the first intranasal inoculation in alternate mice and in control mice. No symptoms developed in the latter group. The number of "takes" in mice that received sodium chloride solution intracerebrally and the streptococcus intranasally was approximately twice as great as in those that received only intranasal inoculations. The results in this series of experiments are summarized in Table 4.

*I am indebted to Dr. C. A. Armstrong, Washington, D. C., for the poliomyelitic virus virulent for monkey and for the Lansing strain of virus adapted to the mouse and to C. W. Jungeblut, New York, for two strains of murine poliomyelitic virus.

It will be seen that (1) the incidence of spasms and convulsions was uniformly much higher in mice that received intracerebral inoculations of the streptococci isolated from conditions characterized by spasms or convulsions (epilepsy, dementia paralytica, and the mouse with convulsions)—spasms occurred in 81, or 88 per cent, and generalized convulsions in 64, or 70 per cent, of 92 mice so inoculated—than in those that received inoculations from conditions in which spasms or convulsions were absent— spasms occurring in 10, or 11 per cent, and convulsions in 2, or 2 per cent, of 89 mice so inoculated; (2) spasms and convulsions occurred in significant incidence following intranasal inoculation of the streptococci isolated in studies of each of the three types of epilepsy; (3) paralysis occurred in 24, or 45 per cent, of 53 mice that

TABLE 3

RESULTS IN MICE FOLLOWING INTRACEREBRAL INOCULATION OF STREPTOCOCCI ISOLATED FROM THE NASOPHARYNX OF PERSONS SUFFERING FROM IDIOPATHIC EPILESPY AND FROM WELL CONTROLS

SOURCE OF STREPTOCOCCI		ANIMAL PASSAGE	STRAINS OR CASES	MICE						
				INOCULATED	SEEN TO HAVE: SPASMS	SEEN TO HAVE: CONVULSIONS	DIED	CULTURED	STREPTOCOCCUS FROM: BRAIN	STREPTOCOCCUS FROM: BLOOD
NASOPHARYNX OF PERSONS SUFFERING FROM IDIOPATHIC EPILEPSY		1	29	17	16	10	20	11	11	6
		2	4	18	16	11	14	10	10	5
		3	1	9	9	7	8	7	5	2
		4	1	6	5	3	7	4	4	2
		5	1	39	38	33	27	24	25	18
		6	1	14	14	11	11	10	9	7
		7	1	15	12	9	10	5	4	3
		8	1	8	8	4	7	7	7	7
		9	1	4	3	2	3	3	3	1
TOTAL		1–9	30	130	121 (93%)	90 (69%)	107 (82%)	81	78 (98%)	51 (63%)
NASOPHARYNX OF CONTROL WELL PERSONS		1	32	23	3	1	9	8	7	4
		2	8	21	0	0	3	1	1	1
TOTAL		1–2	32	44	3 (7%)	1 (2%)	12 (28%)	9	8 (89%)	5 (56%)
EPILEPSY	Heat killed streptococci		4	15	11 (73%)	9 (60%)	8 (53%)	8	0	0
CONTROL			4	12	0	0	0	0	0	0
EPILEPSY	Filtrate of cultures of streptococci		6	22	11 (50%)	4 (18%)	2 (9%)	4	0	0
CONTROL	Filtrate of uninoculated broth		5	10	0	0	0	0	0	0

TABLE 4

RESULTS IN MICE FOLLOWING INOCULATION OF STREPTOCOCCI ISOLATED FROM THE NASOPHARYNX OF PERSONS SUFFERING FROM DIFFERENT TYPES OF EPILEPSY, OF WELL PERSONS AND OF PERSONS SUFFERING FROM DEMENTIA PARALYTICA WITH AND WITHOUT CONVULSIONS, FROM THE BRAIN OF A BABY MOUSE THAT DIED IN CONVULSIONS, AND FROM THE BRAIN AND SPINAL CORD OF MONKEY AND MICE THAT HAD SUCCUMBED TO "VIRUS" POLIOMYELITIS.

Source of streptococci	Animal passage	Strains or Cases	Inoculation	Mice						
				Inoculated	Seen to have		Paralysis	Died	Cultured	Streptococci from brain
					Spasms	Convulsions				
"Grand mal" epilepsy	6 and 7	1	Cerebral	20	16	12	0	15	9	8
			Nasal	11	6	3	0	3	3	2
"Grand mal" epilepsy	1 and 2	1	Cerebral	8	8	7	0	8	3	3
			Nasal	11	5	1	0	2	1	0
"Petit mal" epilepsy	1 and 2	1	Cerebral	9	9	7	0	7	7	6
			Nasal	17	5	3	0	3	3	0
Mentally deteriorated epileptic	1 and 2	1	Cerebral	14	11	10	0	11	8	5
			Nasal	11	6	2	0	1	1	0
Total for cases of epilepsy	1, 2, 6, and 7	4	Cerebral	51	**44**	**36**	0	41	27	22
			Nasal	50	**22**	**9**	0	9	8	2
Dementia paralytica With convulsions	1 and 2	6		19	**18**	**12**	0	12	5	5
Dementia paralytica Without convulsions	1	6		18	3	1	0	14	5	5
Control, well persons	1	6	Cerebral	18	3	0	0	11	6	6
Baby mouse (9 grams) that died in convulsions	1 and 2	1		22	**19**	**16**	0	17	11	10
Poliomyelitic virus	1 to 5	4		53	4	1	**24**	36	25	21

were inoculated with the four strains of streptococci isolated from the brain and spinal cord of a monkey and of mice that died of poliomyelitis following inoculation of virus; this paralysis did not occur in any of 110 mice similarly inoculated with streptococci from sources in which paralysis was absent; and (4) cultures of the brain of 8 mice that developed spasms and that died following intranasal inoculation of the streptococcus from epileptics yielded the streptococcus in only two instances, indicating that the spasms were due perhaps to the absorption of specific neurotoxin from the nasopharynx and from the site of inoculation; the streptococcus was isolated from these areas after death in each instance.

Frothing at the mouth during convulsive seizures was not observed in either mice or rabbits, but sometimes occurred in monkeys during severe convulsive seizures resembling grand mal. Symptoms resembling petit mal and psychic seizures of epilepsy seemingly occurred in mice, rabbits, and monkeys after they were inoculated with the living and heat-killed streptococcus isolated from nasopharynx and blood of persons suffering from epilepsy.

The brain after death in monkeys and rabbits that had succumbed during acute symptoms and in mice that died after spasms had disappeared usually revealed severe congestion, whereas the brain, especially the cerebral cortex, of the mice that succumbed during "status epilepticus" was ischemic, edematous, and usually showed severe cloudy swelling. In no instance was there hemorrhage or abscess formation at the site of inoculation, and grossly visible meningitis was seen in only one mouse in which cultures revealed contamination with E. coli. There were no noteworthy lesions of the viscera.

Sections of the brains of monkeys, rabbits, and mice stained by hematoxylin and eosin, by the Morgan iron hematoxylin method, and for bacteria by a modification of the Gram-Weigert method in which decolorization with alcohol was carried only to a fair blue instead of to the end point, have been examined for lesions and for bacteria.

Those from animals that received inoculations of streptococci isolated in studies of schizophrenia showed only slight or moderate congestion of meninges and cerebral cortex and only slight, widely scattered areas of cellular infiltration. Those from monkeys and rabbits that had been inoculated with streptococci isolated in studies of epilepsy revealed marked congestion and moderate infiltration by leukocytes of meninges in sulci and in superficial layers of the cortex. Sections of the brain of mice that were inoculated with the streptococci from epileptics revealed only slight infiltration of the meninges and the superficial layers of the cerebral cortex, but showed moderate infiltration of the subcortex and severe infiltrations by leukocytes surrounding the choroid plexus and in localized areas of necrosis in the walls of the ventricles. Large numbers of streptococci, chiefly within leukocytes, were found in sections of the brain of animals that died in "status epilepticus" soon after inoculation of streptococci, and only a few or none were demonstrable in animals that died or were anesthetized long after inoculation of living cultures or that died of spasms soon after inoculation of filtrates of cultures. Perivascular infiltration by lymphocytes characteristic of encephalitis was not found regardless of the species of animal or the duration of experiment following inoculation.

The occurrence of maximal lesions, including necrosis, in the walls of the cerebral ventricles in the brain of mice that succumbed to epileptiform seizures following inoculation of the streptococcus isolated from the nasopharynx or blood of persons suffering from epilepsy are in accord with the changes found in the region of the tuber cinereum in the brain of persons suffering from idiopathic epilepsy by Morgan[44] and by Morgan and Gregory[45] and those induced by Morgan and Johnson[46] in the tuber cinereum in the brain of dogs in which epileptiform seizures developed.

ILLUSTRATIVE PROTOCOLS

Protocol 1—A small Macaccus rhesus monkey was inoculated intracerebrally in the right frontal lobe January 7, 1935, with 1.5 ml. of the emulsion of the brain of a mouse that had succumbed to symptoms of polioencephalitis after inoculation of a streptococcus isolated from a water supply of a case of polioencephalitis. The streptococcus, before inoculation into the mouse, was in the tenth rapidly repeated subculture in dextrose-brain broth. Cultures from emulsions of the brain yielded a pure growth of alpha streptococci.

January 9: The animal was excitable, ataxic, and tremulous, and had diminution of vision. The pupils were dilated, and there was slight weakness of the left fore extremity. The condition remained about the same for nine days, when a violent generalized convulsion occurred in which the animal lost its balance, voided urine, and lay unconscious for five minutes; consciousness gradually returned and the animal appeared to be recovered.

February 13: Twenty-six days after inoculation, the monkey was anesthetized and inoculated intracerebrally with 2 ml. of a 10 per cent emulsion of the brains of 3 mice that had succumbed with symptoms of encephalitis after being inoculated with an experimental streptococcal virus strain while in the encephalitic phase.[40]

February 15: The animal was very excitable, ataxic, and tremulous. Its vision was impaired. There was partial paralysis of the right fore and hind extremities. There was little change in the animal's condition until March 5, when it again had a severe generalized convulsion with urination and loss of consciousness resembling a grand mal seizure.

March 6: The monkey was excitable and ataxic; it missed its mark badly on jumping out of and into its cage because of blurred vision and incoordination. It had another violent epileptiform seizure with generalized tonic spasms followed by clonic spasms, frothing at the mouth, urination, and unconsciousness.

March 9: The animal repeatedly had spells apparently of momentary loss of consciousness, in which it sometimes fell to the floor without spasms; these spells resembled petit mal.

March 10 and 11: Ataxia and hyperirritability continued, resembling grand and petit mal.

March 12: The monkey was reinoculated with the emulsion of the brains of 2 mice that had succumbed to two further passages of the same virus diluted three hundredfold in sodium chloride solution.

March 13: The animal was ataxic and hyperirritable, and on jumping from its cage it had a severe generalized convulsion resembling grand mal.

March 18: The animal seemed better, and no convulsions were noted for eleven days.

March 29: The animal was inoculated with a 10 per cent emulsion diluted one thousandfold of the brains of 2 other mice that had succumbed to further successive passages of the experimental virus. The animal remained about the same, and no spasms were noted until April 8, at which time a violent seizure recurred.

April 9: The monkey was less irritable; however, it missed its mark badly in jumping out of and into its cage, and when observed in its cage it had "lapses" resembling petit mal.

April 12: There was a recurrence of hyperirritability. The animal was more ataxic; generalized spasms did not occur, but it had severe tremors of its head associated with mild clonic spasms. The temperature was 104.8°F.

April 13: There was now great weakness of hind extremities and ptosis of the eyelids; the temperature was 103.4°F.

April 14: The tremors continued, but no spasms were noted. The animal was lethargic, and great weakness of hind extremities had developed. The temperature was 97°F.

April 15: The extremities were spastic, and they were so weak that the animal could not stand.

April 16: Condition was about the same, but on prodding mild generalized spasms developed. The temperature was 98° F. The animal was anesthetized to death with ether. There was moderate congestion of the cerebral cortex. The cerebrospinal fluid was greatly increased in amount but was clear. The cerebral ventricles were dilated. There was a small cyst at the site of intracerebral inoculation. Cultures from the pipetting of the brain proved sterile.

Protocol 2—A medium-sized Macaccus rhesus monkey was inoculated intracerebrally December 20, 1936, with 1 ml. of a 1:200 dilution of a dextrose-brain broth culture of a streptococcus isolated from the blood of a patient who suffered from nocturnal epilepsy.

The animal remained well until December 25, when severe tremors and weakness of the hind extremities developed.

December 26: The animal had recurring seizures of generalized tonic and clonic spasms in which it lost its balance and fell to the floor; in severe seizures it voided urine, sometimes frothed at the mouth, and became unconscious for five minutes or more after which consciousness returned, and spasms disappeared. The attacks of spasms recurred at frequent intervals but in progressively milder form for ten days; they then disappeared as the animal recovered. It was observed until January 29, 1937, and no additional spasms were noted.

Protocol 3—A medium-sized Macaccus rhesus monkey was inoculated May 20, 1935, with the Berkefeld filtrate of a 5 per cent emulsion of the brain and spinal cord of a monkey that had succumbed to an intracerebral inoculation of experimental virus derived from a hemolytic streptococcus originally isolated from a case of endocarditis and which had been changed into an alpha streptococcus having neurotropic cataphoretic velocity and virulence and from which a filtrable virus was produced.[40] The experimental virus used for inoculation had been passed consecutively through 8 series of mice nearly all of which developed encephalitis. Cultures from the filtrate inoculated proved sterile. The monkey's temperature was 101°F. Of the filtrate 1.5 ml. was injected intracerebrally, 2 ml. intraspinally, 10 ml. intravenously, and 10 ml. intraperitoneally.

May 23: Cultures from the spinal fluid obtained at the time of inoculation were sterile. Gram-safranine stains of the centrifugated sediment of the spinal fluid revealed lymphocytes and a few gram-positive diplococci, and a short-chained streptococcus was isolated in dextrose-brain broth. The animal was fussy, and its temperature was 104°F. The injections were repeated.

May 24: The animal was hyperirritable, and the face was flushed. The temperature was 104.6°F.

May 26: The animal appeared abnormally quiet and half-dazed. The temperature was 101.6°F.

May 27: The animal acted strangely and kept looking to the right seemingly at imaginary objects; when prodded it suddenly seemed to realize its surroundings and became excitable and tremulous after which its strange action returned. Spinal puncture revealed slightly turbid spinal fluid due to lymphocytes, and in the centrifuged stained sediment a few unmistakable gram-positive diplococci were found. The temperature was 104°F.

May 28: 8 A.M.—Most of the time the animal did not seem to realize what was going on and still kept looking wildly about at imaginary objects. 6 P.M.—The animal was semicoma-

tose, in a generally rigid state resembling catalepsy, and had developed marked weakness, especially of the fore extremities. Respirations were slow, and heart action was very rapid. The temperature was 100.8°F. Spinal puncture revealed clear fluid and no bacteria.

May 29: Cataleptic symptoms were less marked. The animal lay on its side alternately in relaxed and rigid states. There was continual vertical nystagmus and marked drooling of saliva. It had repeated mild generalized clonic spasms in which the animal opened its mouth widely as spasms of the muscles of the jaw and tongue occurred. The animal was anesthetized to death. There was severe congestion of the brain; a small cyst was found in the right frontal lobe at the point of intracerebral injection. Cultures from pipettings of brain substance admixed with spinal fluid proved sterile. Sections of the brain revealed mild perivascular and parenchymatous round cell infiltration.

Protocol 4—A large rabbit weighing 2,850 gm. was inoculated intracerebrally January 27, 1936, with 1 ml. of the saline suspension of the nasopharyngeal swabbing of a patient suffering from severe epileptic seizures.

January 28: 8 A.M.—Tremors of masseters and mild clonic spasms of the muscles of the face and ears were noted. 9 P.M.—The animal was ataxic, respirations were greatly increased, weakness of hind extremities had developed, and mild generalized clonic spasms occurred at intervals.

January 29: 8 A.M.—The tremors were more marked and clonic spasms occurred frequently. 11:30 A.M.—A generalized spasm resembling grand mal occurred. 2 P.M.—While being watched, the animal suddenly leaped forward, fell to its side in violent tonic spasm followed by severe generalized clonic spasms. It voided urine and then lay unconscious with stertorous respiration for a short time. During this period it did not respond to stimuli. As consciousness returned, the animal rose to its feet; it was then free from spasms for two hours, when suddenly a similar but more violet seizure occurred, during which it died in generalized tonic spasms from respiratory failure. Necropsy revealed severe congestion of the brain, slight clouding of meninges, no mark at the site of intracerebral injection, and no lesions of the viscera. The streptococcus was isolated from the brain. The blood proved sterile.

Protocol 5—A white rabbit weighing 2,000 gm. was inoculated intracerebrally June 1, 1935, at 10 A.M. with 0.5 ml. of a sodium chloride solution suspension of the heat-killed streptococcus isolated from the nasopharynx of a patient suffering from severe epilepsy. At 2 P.M. and 5 P.M. marked tremors of masseters were elicited by palpation. At 8 P.M. the animal, while sitting quietly in cage, suddenly cried out as it developed a violent convulsive seizure. Spasms were tonic at first, then clonic as it apparently lost consciousness and stertorous, extremely irregular respiration developed. Shortly following this the animal regained consciousness and was again free from spasms; tremors of masseters continued, however.

June 2: 9 A.M.—The respirations were rapid; the animal was ataxic and tremulous, and tremors of masseters continued. 12 M.—The animal again developed a violent convulsion and died of respiratory failure with head retracted and extremities rigidly outstretched. Necropsy revealed severe congestion of the cerebral cortex and no mark at the site of injection. Cultures from brain and blood were sterile.

Protocol 6—A white and gray rabbit weighing 2,000 gm. was inoculated intracerebrally August 28, 1936, with 0.1 ml. of a culture of the streptococcus in autoclaved chick embryo medium isolated from the nasopharynx of a patient suffering from manic-depressive psychosis.

August 29, 30, and 31: The animal was extremely excitable and tremulous. It apparently imagined that it was about to be attacked since it repeatedly jumped violently about in its cage, and unknowingly jumped out of the cage when the door was opened. During quiet intervals the waving of one's hand over its body caused it to jump violently about.

September 1: The animal was greatly improved. It was anesthetized with ether and reinoculated. Following this inoculation, it again became hyperirritable and instead of being frightened by imaginary objects it became extremely cross and it repeatedly threatened to charge.

September 3: The injection was repeated. The symptoms persisted, and the animal was found dead September 5. Necropsy revealed moderate congestion of the brain, no meningitis, no mark at the site of intracerebral inoculation, and no lesions of the viscera. The streptococcus was isolated from the brain in dextrose-brain broth. The blood proved sterile.

Protocol 7—A white mouse weighing 30 gm. was inoculated intracerebrally June 6, 1946, at 8 A.M. with 0.03 ml. of a 10:1 sodium chloride solution suspension of a streptococcus from a dextrose-brain broth culture of the nasopharynx of a patient suffering from idiopathic epilepsy and from the brain of a mouse that had succumbed to convulsive seizures following inoculation of this strain in the fifth mouse passage. The streptococcus before inoculation into the mouse was derived from growth in extremely high dilution and was in the second subculture. At 8 P.M. slight tremors had developed and respirations increased. At 9:35 P.M. its fur was ruffled and tremors were more pronounced. While it was being observed, recurring tonic and clonic spasms developed, beginning in the face and jaws and extending rapidly to the right foreleg and right hindleg. These were followed by generalized spasms in which the animal fell to the left, then turned on its back while having sharp clonic spasms of the muscles of the jaw and neck, and pulling its head sharply to the right and voiding urine. Following this, it lay limp, insensible to stimuli for fifteen seconds, when spasms recurred. It was observed continuously for one hour, during which time it had severe recurrences of tonic and clonic spasms resembling "status epilepticus."

June 7: 4 A.M. and 7 A.M.—Attacks of spasms recurred at short intervals but were less severe. Mild attacks of spasms continued through June 12, and the animal was found dead June 13.

The characteristic cloudy swelling and ischemia of brain was found at necropsy. The meninges were wet and shiny. There was no mark at the point of injection. The viscera were normal. Cultures of the brain were negative on blood agar but yielded the streptococcus in dextrose-brain broth. The blood proved sterile.

Protocol 8—A white mouse weighing 25 gm. was inoculated intracerebrally June 11 and 12, 1946, at 9 A.M. with 0.03 ml. of a 20:1 suspension in sodium chloride solution of the heat-killed streptococcus isolated from the brain of a mouse inoculated with the strain isolated from persons having epilepsy in the seventh mouse passage.

June 12: 9:30 P.M.—Severe tremors and slight spasms had developed. 10:30 P.M.—The animal had a generalized convulsion.

June 13: 4 A.M. to 10 A.M.—The animal was seen to have almost continuous tonic and clonic spasms resembling "status epilepticus," and at 11:45 A.M. the animal died during a severe seizure. Necropsy revealed moderate cloudy swelling of brain, but there were no other lesions. Cultures of brain and blood proved sterile.

Protocol 9—A white mouse weighing 30 gm. was inoculated intravenously June 3, 1946, with 0.5 ml. and intracerebrally with 0.03 ml. of a filtrate of a dextrose-brain broth culture of the streptococcus from the end point of growth of a serial dilution culture from the nasopharynx of a patient suffering from severe epilepsy.

June 4: 4:30 A.M.—The animal seemed well and was free from spasms. 10 A.M.—As animal was observed, undisturbed, it suddenly developed violent tonic and then clonic generalized convulsions lasting for about fifteen seconds. It then lay quietly, insensible to stimuli for about ten seconds, when it suddenly became rigid with severe tonic and then clonic spasms. It again lay quietly on its side, breathing violently for a few seconds, insensible to stimuli when a third similar seizure resembling

"status epilepticus" occurred, in which it died. Moderate congestion of the cerebral cortex was found at necropsy. Cultures of brain and blood proved sterile.

Protocol 10—A white mouse weighing 25 gm. was inoculated intranasally on June 18, 19, and 20, 1946, with 0.1 ml. of a 20:1 suspension of the live streptococcus after six animal passages and originally isolated from the nasopharynx of persons suffering from severe epilepsy. In addition, it was inoculated intracerebrally with 0.03 ml. of sterile sodium chloride solution immediately after the first intranasal inoculation.

June 21: Until this time the animal remained seemingly well. 7:15 A.M.—At this time of the day after the third intranasal inoculation, it was seen to have violent generalized tonic and then clonic spasms, in which the animal was thrown violently about as the head was drawn sharply backward and as extremities were outstretched in tonic spasms. This attack was followed shortly by rapidly recurring clonic spasms, grinding of teeth, and voiding of urine. The animal then lay limp, insensible to stimuli for ten seconds, when slight and later violent spasms recurred. Seizures resembling the one described then recurred in rapid succession for two hours, after which spasms became continuous resembling "status epilepticus" in which the animal died four hours later. There was slight congestion and cloudy swelling of the brain; the lungs and other viscera were normal. Cultures on blood agar from brain and blood proved sterile, and cultures from the brain in dextrose-brain broth yielded a pure culture of streptococcus.

COMMENTS AND SUMMARY

The occurrence of spasms or convulsions and of disorientation in monkeys in low incidence following inoculation of natural and experimental poliomyelitic and of encephalitic virus and neurotropic streptococci isolated from these and other sources, and the production of respective, more or less characteristic, symptoms in a high incidence in monkeys, rabbits and mice with alpha streptococci isolated from nasopharynx or blood of persons suffering from epilepsy and schizophrenia is reported.

The seizures, especially in mice following inoculation of the streptococci isolated from nasopharynx or blood of persons suffering from epilepsy, resembled those that occur spontaneously in patients in the periodicity, in the suddenness of onset of recurring seizures, in the rapid increment of spasms during attacks ending often in generalized convulsions, a falling to the side, voiding of urine, loss of consciousness, and rapidity of apparent recovery from recurring attacks.

Spasms and convulsions occurred in mice in about equally high incidence on intracerebral, and in comparable low incidence on intranasal, inoculation of the streptococci isolated from nasopharynx of persons suffering from different types of epilepsy — grand mal, petit mal, and psychomotor seizures with mental deterioration without convulsions—but due to prior seizures typical of epilepsy, and from epileptics in whom seizures were controlled by the administration of anticonvulsant drugs—phenobarbital or dilantin or both.

The symptoms in animals that followed the inoculation of the streptococcus isolated from persons suffering from idiopathic epilepsy and dementia paralytica were obviously more convincing proof of etiologic relationship than those following inoculation of the streptococci isolated from persons suffering from schizophrenia.

The occurrence of spasms and convulsions in the baby mouse shown to be due to the streptococcus whose mother had been inoculated intranasally early during gestation with the streptococcus from an epileptic should not be interpreted as indicating either an in utero transmission of the streptococcus or an inherited predisposition, but should rather be interpreted as due to chance nasal-to-nasal infection after birth.

The data obtained indicate that persons suffering from idiopathic epilepsy and schizophrenia harbor in their nasopharynx and sometimes in their blood respective specific types of alpha streptococci, and that the symptoms characteristic of these diseases may be due in large part to the absorption of respective specific neurotoxic substances produced by the streptococci in nasopharynx or other atria of infection in addition to the localization and infection in the brain by the respective streptococci.

The negative cultures from the brain of animals that died from convulsive seizures resembling "status epilepticus" long after intracerebral or intranasal inoculation of the streptococci, the sharp drop of streptococcal antigen in skin or blood with concomitant sharp rise of specific antibody and transient disappearance of symptoms in patients following grand mal seizures, and the subsequent day-by-day increase of antigen (to be reported elsewhere) support the view generally held that the seizures and other symptoms in epilepsy are of toxic origin and that the streptococcus which we have isolated may be a common source of the specific neurotoxin.

A week or ten days after intracerebral, and especially after intranasal, inoculation of material containing the respective specific types of streptococci and negative cultures from the brain of persons for which the "neurotoxin" and the respective specific types of streptococci have predilection or elective affinity, animals may become sensitized so that extremely small amounts of the "neurotoxin" —too small to be detected in serum or blood—and small numbers of streptococci suffice to produce the respective characteristic symptoms.

The common occurrence of the respective specific types of streptococci in the blood of epileptics, especially shortly before or during grand mal seizures, and their occasional presence in the blood of persons suffering from severe schizophrenia are in accord with this idea.

The importance of heredity in relation to the presence of specific types of streptococci in epilepsy and schizophrenia, their relation to the electroencephalogram,[43] the nature of the respective streptococcal "neurotoxins," and active and passive immunization with specific streptococcal vaccines and thermal antibodies[47, 48] are under study.

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Book of the Month—A Report

INTERNAL MEDICINE in GENERAL PRACTICE*

In this relatively small volume, the basic principles and the practical considerations of the everyday problems in internal medicine are clearly and briefly reviewed. Quick reference with sensible application for the busy physician are two main functions of the text.

Controversial material and lengthy discussions of diseases rarely encountered are omitted, while diagnostic and therapeutic methods most readily adaptable for use in general practice have been stressed by the author.

An appropriate bibliography is included for those who wish more extensive detailed reading. Liberal use is made of illustrations, and many tables and charts are included in order to emphasize and simplify various topics.

Accurate diagnosis early in disease is a point the author repeatedly emphasizes when discussing the fundamentals of diagnosis in the first portion of the book. The author includes laboratory aids and new diagnostic technics, but cautions that these facilities are not substitutes for good clinical judgment based on a careful history and a thorough physical examination.

In view of the recent popularity of psychosomatic medicine, especially since World War II, a chapter on psychiatric disorders is included in this edition. Dr. McCombs feels that every physician should understand and know the manifestations of the more common psychiatric disorders, so that he can correct or forestall a large portion of these disorders by treatment which is often quite surprisingly simple.

*Internal Medicine in General Practice. By Robert Pratt McCombs, B.S., M.D., F.A.C.P., Professor of Medicine and Director of Postgraduate Teaching, Tufts College Medical School; Senior Attending Physician, The Joseph H. Pratt Diagnostic Hospital; Diplomate of the American Board of Internal Medicine. 697 pages, with 122 illustrations and 15 tables. Philadelphia, W. B. Saunders, Company, 1947.

The author emphasizes systematic methods of examination for any disease encountered, giving analyses of the many associated signs and symptoms, and discussing both their anatomic and physiologic interpretations.

No book of medicine is of practical value unless maximum consideration is given to therapy. In this text, Dr. McCombs reviews in detail the different therapeutic approaches: restriction of activity, dietary management, the use of drugs, etc., are all discussed at length. Not only "time tested" technics, but also the recent advances in therapy are included, as well as those little "common sense suggestions" which are usually learned only through years of experience.

The subject of peptic ulcer is given considerable attention since it is one of the most common diseases of the digestive tract, while another type of great interest which is given lucid explanation is the study of the liver and related diseases.

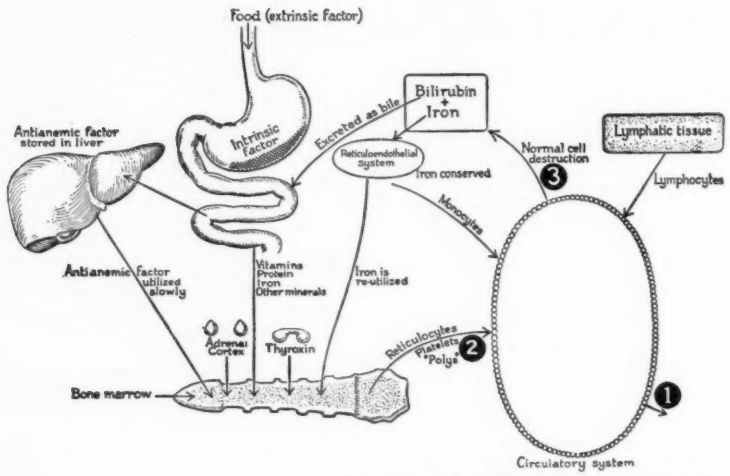
Immediately following the intestinal disorders are chapters on nutritional deficiencies, anemias, blood dyscrasias, and allied diseases.

Throughout this section there are excellent photographs and colored illustrations of the deficiency states. Also included is a pertinent chart summarizing the important information concerning the vitamins.

In the second half of the book, the author takes up the infectious diseases, the rheumatic diseases, and the uses and abuses of the sulfonamides, penicillin, and streptomycin.

Again, as in previous chapters, an analytic survey of symptomatology is made and the role of important bacteriologic investigation discussed.

In view of the importance of chemotherapeutic agents, the author has gone into considerable detail concerning each with reference to their effect on



From McCombs: Internal Medicine in General Practice.

The formation of the blood cells and the mechanisms of the development of anemia. Anemia results: (1) when the integrity of the circulatory system is broken (*acute and chronic hemorrhage*); (2) when there is decreased production of blood by the bone marrow, such as occurs when there is a lack of one or more of the red cell-building elements (*deficiency anemias*), when there is invasion of the bone marrow by tumor cells (*myelophthisic anemias*) or when the function of the bone marrow is depressed by toxins (*toxic and aplastic anemias*); and (3) when there is an increase in the normal rate of cell destruction (*hemolytic anemias*).

specific bacteria. In addition, there are several summarizing charts to help one see at a glance the advantages and disadvantages of the drugs' action on individual organisms.

In the final section of the text, the author takes up the chronic rheumatic diseases, endocrine disorders, vascular disturbances of the extremities, and miscellaneous conditions.

While writing this book, Dr. McCombs was thinking constantly of its practical application by the physician, and he has exerted great effort to clarify and simplify subjects which are by nature very complex. In this aim, he has succeeded in providing methods for more accurate diagnosis and better management of those problems with which the physician is confronted in his daily practice.

RECEIVED THIS MONTH

MINOR SURGERY, By Frederick Christopher, B.S., M.D., F.A.C.S., Associate Professor of Surgery at Northwestern University Medical School, Chief Surgeon, Evanston (Illinois) Hospital. Ed. 6. 1,058 pages with 937 illustrations on 595 figures. Philadelphia, W. B. Saunders Company, 1948. Price $12.00.

A MANUAL OF PHARMACOLOGY, and Its Applications to Therapeutics and Toxicology, by Torald Sollmann, M.D., Professor Emeritus of Pharmacology and Materia Medica in the School of Medicine of Western Reserve University, Cleveland. Ed. 7. 1132 pages. Philadelphia, W. B. Saunders Company, 1948. Price $11.50.

A MANUAL OF CLINICAL THERAPEUTICS, A Guide for Students and Practitioners, by Windsor C. Cutting, M.D., Professor of Therapeutics, Stanford University School of Medicine, San Francisco. Ed. 2. 712 pages with 30 illustrations. Philadelphia, W. B. Saunders Company, 1948. Price $5.00.

MEN OF MEDICINE

FOR SERVICE TO THE COMMUNITY

STOCKILY built and six feet tall, with a friendly, weatherbeaten and round, red face, Dr. Archer Chester Sudan likes the rugged life of the out of doors. With an easy-going, cheerful manner, he likes all kinds of people, and likes to help them when they are in trouble. These are some of the reasons why practically overnight he left an enviable teaching and research position at the University of Chicago to spend twenty years in rural Colorado as a general practitioner.

This choice and the devotion he gave to the treatment of the ills of the rural small town people under his care have earned him the first General Practitioner Award of the American Medical Association. Dr. Sudan was selected for the association's newly created gold medal from among hundreds of practitioners whose names were submitted for consideration. The medal was officially presented to him at a special ceremony in his honor during the interim session of the association at Cleveland, January 7. The presentation was made by Oscar Ewing, director of the Federal Security Agency.

This award, similar to the American Medical Association's Distinguished Service Medal, which has been given annually since 1938 for scientific advancement in the field of medicine, is designed especially to honor a general practitioner who has served as a family physician and who, in that capacity, has received the recognition of his community. The award is known as "the medal of the American Medical Association for exceptional service by a general practitioner." The award includes not only a medal, but a certificate indicating the reasons for the award.

Among the careers of all the practitioners whose names were submitted for the award, none could compare with that of Dr. Sudan. He had overcome obstacles and endured hardships that would have discouraged and wrecked anyone less vital and cheerful.

In accepting the award, Dr. Sudan said:

"The good will doctors enjoy today is the heritage of past generations of general practitioners.

"Therefore, I accept this award as your recognition of thousands of general practitioners. It is a great honor, indeed, to have been selected from among hundreds of equally meritorious candidates to receive this, the first such award. Words cannot express my gratitude.

"General practitioners, today as in the past, are doing their utmost to maintain and enhance their service to the public. They believe, and I believe, that the average American deserves a better-than-

average family doctor. Modern medical schools recognize this fact, and are constantly exerting themselves to produce better doctors, better general practitioners.

"Also, the public is awakening to the fact that the doctor, in turn, deserves modern facilities with which to work, including modern hospitals. I believe this is a community responsibility. I am happy to know that many small towns and rural areas are now building their own community hospitals with their own community funds. As these hospitals develop and provide facilities for the doctor, modern general practitioners will welcome the opportunity to practice in such areas. And that will solve the biggest problem in the distribution of medical care, one of the biggest problems in improving rural health.

"I have practiced among the far-flung ranches of the Colorado mountains for more than twenty years. Those years convinced me that we must personally keep close to our people. If we do our work right, we establish closer contact with the public than does any other profession. As we do this, our efforts to cure, to alleviate, or to comfort, become more efficient."

Dr. Sudan's choice of the career of a country doctor in one of the most rugged areas of the United States was done with the greatest deliberation. At the University of Chicago his work was rated highly and he had given every promise of greater success both as a teacher and research scientist. But he made a choice that was more nearly suited to his fundamental makeup.

Dr. Sudan was born in Sioux Falls, South Dakota, August 15, 1892. He entered the University of Chicago College of Medicine in 1916, receiving the bachelor of science degree in 1922 and the degree of master of science in 1923. He transferred to Rush Medical College on a Laverne Noyes scholarship, and received the degree of medicine there in 1926. After an internship at the Denver General Hospital, Denver, Colorado, he joined the faculty of the University of Chicago. In collaboration with Drs. Lester R. Dragstedt and K. Phillips he was the author of a number of studies in the pathogenesis of tetany.

But whenever he could get away he would pack his fishing tackle and head for the country. On a fishing trip to Colorado he stopped in a drug store at Kremmling and asked about a good spot to fish. Kremmling is a town of 567 population about 70 miles northwest of Denver on U. S. Highway No. 40 and the old Denver and Salt Lake Railroad. It is in Grant County, which has a population of about 4,000. The town is at an altitude of about 7,500 feet in a mountainous country of striking beauty with passes through the mountains from one town to another ranging as high as 11,000 feet. "No one," Dr. Sudan says, "can imagine the splendor of the country. He must see it."

While he was chatting with the druggist, a villager ran into the store and said that he had heard there was a doctor in town. When the druggist had introduced him to Dr. Sudan, he said there were four children on the outskirts of the town who were all in bed with serious cases of tonsilitis. Would the doctor come quickly for the need was urgent? Dr. Sudan forgot about fishing and followed the villager to the home.

From the village and others, he learned there was great need for medical care throughout the whole area. There were no doctors and no hospitals for miles. There was a great amount of chronic and acute illness and improperly healed injuries among the ranchers, laborers, coal miners and hard rock miners. Many miners had been victims of explosions and fires. Ranchers and ranch laborers had suffered many severe injuries. The hard rock miners, their lungs coated with dust, died at an early age. There were babies to be delivered and old injuries to treat.

All this strongly appealed to Dr. Sudan's instinct and training. He cleared up the four cases of tonsilitis and stayed on to treat more patients. He informed the University of Chicago that he wanted his leave extended for a year. This was granted, but at the end of the year, he handed in his resignation. He planned never to return to the life of researcher and teacher in the university.

The winters are severe in the Kremmling region. Temperatures at times go to 50 below zero, and hover around 20 to 40 below a great part of the winter season. Snow fall is heavy. The cold and the snow made traveling to patients a great prob-

ARCHER
CHESTER SUDAN,
M.D.

lem. Often Dr. Sudan's car would get stuck in a snow drift or skid off the road. Frequently he would have to shovel out a pathway for his car through the snow or tear out a post from the roadside and hoist it back on the road.

U. S. Highway No. 40 was kept clear most of the winter, but the side roads very often were impassable. On those occasions ranchers would take him across the country on their bobsleds. Each rancher would transport him across his own land to an adjoining neighbor, where the neighbor would meet him and take him in the same fashion to the next rancher. Although most of the patients lived in a radius of eight or ten miles from Kremmling, Dr. Sudan, with roadways blocked, often had to travel long circuitous routes to get to them. Some trips took two to four hours each way. Sometimes a patient in need of hospital care had to be brought back to Kremmling and shipped on the highway or railroad to Denver.

Dr. Sudan would carry adequate equipment with him. His biologicals he packed in thermos bottles to keep them from freezing during severely cold weather. He had to do a considerable amount of improvising for usable equipment. He had a shop and laboratory at his home, and could work

OSCAR R. EWING
(left) and
DR. A. C. SUDAN

with his hands fairly well. If, when he arrived at the home of a patient and a bedside table was needed, he would build one on the spot out of packing boxes. If a bedpan was needed he would make it out of the most likely kitchen utensil. An inhaler for a croupy baby he would construct out of a coffee pot or a bucket.

In the crude settings of villagers' and ranchers' homes he performed many difficult surgical operations. During his twenty-one years at Kremmling he has delivered a total of 1,000 babies, 700 of them in the home.

His fees were around $2 and $3—the latter figure frequently collected for a complete physical examination. When the patient had no money Dr. Sudan would receive potatoes, eggs, butter, and beefsteaks.

It was not long after his arrival that he became a leader in the community. His philosophical counsel was widely known throughout Colorado's "Western Slope." He gave advice freely—whether a young daughter should marry or finish school first, or whether a rancher should buy an adjoining tract of land, sell his stock at the present market, or hold for higher prices. He would attend as many of the public gatherings as he could, take part in the discussions and enjoy the fun of dances and jamborees.

The ranchers in the area are individualists. They do not want too much aid from the government and like to rely on their own resources. Even in the more outlying areas, according to Dr. Sudan, the people expect good medical care. They hear about the miracles of medicine performed in the big city hospitals and expect the country doctor to do as well. So under his guidance and leadership they built a twelve-bed hospital at Kremmling. They recognized readily that the hospital was their responsibility and took an active part running it. It was not too hard to raise money for it. At the Sunday night social gatherings in various parts of the county, where Dr. Sudan was always a welcome guest, the people would dig down in their jeans and hand the money over.

There was, in fact, stiff competition among the donors. If the people of Willowfork raised $35 or $40 at one of their gatherings, the people of nearby Troublesome would soon hear about it. They saw

to it that Willowfork would not get ahead of them, and the next social gathering at Troublesome would put $175 in the collection plate.

The hospital was a boon to the general practitioner, and Dr. Sudan believes that even in such rugged country as the Kremmling area a young doctor could be happy in general practice if he had such facilities. He believes that the enthusiastic youngster, graduating from his internship, wants, probably more than anything else, facilities that will permit him to apply his training. As more hospitals such as the one in Kremmling are established, more doctors will want to practice in rural communities. He recommends that more medical schools place greater emphasis on the preparation of their students for experience such as they face if they select rural areas for their practice.

Not only did Dr. Sudan's reputation as a physician spread throughout the state among men of his profession but he soon established a reputation for his ability to organize and direct community affairs. In 1946 the Colorado State Medical Society named him president of their organization. This was the first time in the society's 77-year history that a physician from a completely rural area had been selected for that office. When Dr. Sudan was inaugurated for that office during the state meeting in Estes Park, Dr. Dragstedt was present in the audience. He expressed the opinion that when the Colorado physician chose rural practice as a career, research was definitely the loser.

Dr. Sudan has gone much further than providing treatment and care to patients of the area. He was always conscious of the importance of preventive medicine. During his years of rural practice he educated people for better health. His work has been significant in the progress of health education in the state. He was also interested in general education as well, and for many years was a member of the school board in Kremmling.

As a preventive health measure he believes that medical societies should take the lead in improving working conditions and safety programs in agriculture and industry.

Dr. Sudan was nominated for the General Practitioner Award by the Colorado State Medical Society. The nomination was presented to the American Medical Association by Dr. Bradford Murphey, chairman of the state society's board of trustees.

Dr. Sudan is married and has one son, Archer Chester Sudan, Jr., is 19 years old.

LEAD POISONING

ALTHOUGH BAL (British Anti-Lewisite) has been found highly effective in the treatment of acute poisoning caused by toxic quantities of arsenic, antimony, bismuth, and certain other substances, no similar therapeutic effect has yet been reported in cases of lead poisoning. Indeed, one group of investigators found that BAL was actually deleterious in the treatment of lead poisoning. Since plumbism has such a seriously high incidence and severity, further therapeutic trials with BAL have certainly been justified. Telfer, of the United States Public Health Service, has had encouraging results.

BAL combines with arsenic, pulls it out of the tissues, and holds it in combination during excretion, so that the arsenic cannot produce toxic effects while in circulation. Investigators have hoped that BAL would perform a similar function in the treatment of lead poisoning.

Telfer's study embraces only one case; however, this patient had a definite history of exposure, as well as typical symptoms. After the administration of the BAL, the concentration of lead in the urine rose to levels which indicated a toxic dose. Heavier excretion of lead occurred during the second course of BAL. The patient responded well to treatment, was discharged in good health, although the "lead line" persisted in his gums. The author concludes that BAL might well have a place in the treatment of lead poisoning and suggests further study.

EDITORIALS

THE TRAINING AND QUALIFICATION OF AN INTERNIST

Someone, half seriously and half jokingly, has said that an internist was just a family physician with a reputation. As a matter of fact, that is a fair statement of the situation prior to the advent of the "specialty boards."

In most instances those men of broad medical interests who developed skill in diagnosis in obscure cases of internal disorders and achieved a reputation as consultants, thereby became our first internists. Their skill was not a matter of divination; it was based upon a very broad and extensive general experience, together with an ability to make rapid diagnostic correlations of seemingly unrelated phenomena. There were men like Sir James Mackenzie and Kussmaul who derived their skill from general practice; others like Osler who had a long experience in the dead house. There were even surgeons like Harvey Cushing who could qualify in this field, apart from the therapeutic procedures they employed in their work.

In recent years this *qualification by reputation,* for expertness, based on broad and long experience, has been replaced by the method of *qualification by examination,* by specialty boards, of which there are fifteen, loosely bound together by an Advisory Board. These boards derive their authority from the recognized national societies in each specialty and the American Medical Association. Each board establishes its own minimum standards for competence in its special field, and rigidly prescribes the type of training which must precede admission to the qualifying examination.

Thus a rigid structure has been set up, which by indirection has placed our educational system and the specialists themselves in a strait jacket. Vigorous protests are heard from the educators on one hand, and clamorous outcries from would-be specialists on the other, when they find difficulty in fitting themselves into these rigid patterns. Add to this the fact that the most successful candidate in an examination is likely to be the man most recently come from academic halls and the wards of our teaching hospitals, and who, therefore, has a great advantage over the man of long experience who may have acquired a vast reputation as a consultant among his fellows in practice. Furthermore it should be recognized that no written examination is likely to reveal that quick, penetrating, almost intuitive insight which enables the master diagnostician to appreciate the subtle interrelationships by which a diagnosis is reached in obscure and puzzling cases.

In this situation one is reminded of the words of Clifford Allbutt, written in 1905:

"It will not be supposed that I ignore the limits and diversities of human faculty, for to one may be given manual dexterity, to another sagacity of observation and inference; nor forget the field of Medicine is so vast that for the narrowness of man's capacity it must be divided: what I urge is that the limits be by personal choice on natural lines, not by the survival of medieval rules, even in their own day vicious, whereby we have made an idol of this divergence, telling each physician, each surgeon, that he shall not follow the bent and growth of his own faculties and the intimate tracks of nature, but that, whatever his capacities and occasions, thus far he shall go and no farther; in the use of his natural gifts he shall be fettered by an artificial rule. Every wise man learns, but too soon, his own defects, his own limits, his own bents, and the natural economy

they impose upon him; but to maintain separate Colleges to intensify schism, to separate the man who treats a disease with one remedy from the man who treats the same disease with another remedy, to distribute half a malady to one practitioner, to another the remnant . . . is contrary to nature, art, and common sense."

In the face of the existing situation in American Medicine, in which we see such rapid and progressive differential specialization, the immediate and crying need is for integration. In making this integration the internist must take the leading role. Integration is his special function, and he must understand that the sick person is more than the sum of his anatomic parts, that he is an individual organism whose ill-being is the expression of its struggle to adapt itself to environmental stresses, internal or external, physical, psychologic, economic, or social. Such a man must synchronize and harmonize the efforts of his specialized brethren much as the conductor of an orchestra does in producing a symphony.

Just as a great conductor may or may not be a solo artist, may or may not be a great composer, so the great internist may or may not have special skills, may or may not have made original discoveries; each of these integrators must have an artist's appreciation of the relations of the parts to the whole. Is it not time that we inquire into the present regimen of training prescribed for internists with a view to determining its success in this direction?

W. S. McC.

MID-YEAR A.M.A. MEETING

The first midwinter session of the American Medical Association closed in Cleveland, January 8, as a qualified success. The meeting was projected only last June, and the intervening months were apparently too few in which to promote the interest and attendance of general practitioners which was originally contemplated.

In spite of what was to all but official sources a disappointing attendance, the meeting had many excellent features. The first two days were occupied by sessions of the Eighth Annual Congress on Industrial Health. Good papers were presented at these meetings but the majority were scarcely suitable for the greater proportion of the general practitioners for whom the session was planned.

During the first two days when the House of Delegates was also in session, attendance at the Scientific and Commercial Exhibits was poor. This was unfortunate because most of the scientific exhibits were of high caliber and the commercial exhibitors felt badly let down. On Wednesday and Thursday, however, when the regular scientific meetings started, the situation was quite different.

The two days of scientific sessions contained symposiums, panel discussions, and individual lectures. These were, with few exceptions, calculated to give general practitioners information most wanted concerning the everyday problems of practice. Since a future midwinter session has been announced for December of 1948 in St. Louis, an expansion of this type of presentation would be helpful, especially the first two days.

Other features of interest were the Cancer Detection Center operated in the scientific exhibit, and the Clinical Demonstrations and Conference in Dermatology, Diabetes, and Conservation of Hearing. These were operated with skill and presented worthwhile information.

The scientific exhibits were smaller in number than is customary at an Annual Session of the A.M.A. Some of them had been shown before at other meetings, but several were new. Awards were not given for the exhibits. On the whole, those which were designed primarily for general practitioners seemed more appropriately adapted to the purposes of the meeting.

All in all, this first Interim Session conducted an interesting experiment. Whether it will be continued beyond next December's session presumably depends on the attendance at that meeting and the desires of all concerned.

TALCUM POWDER GRANULOMA

TALC GRANULOMA is a serious and not infrequent postoperative complication. It is of more than just academic interest. Numerous authors have recognized the dangers incident to using talcum powder in surgical gloves. The seriousness of the procedure was emphasized a few years ago by Weed and Groves, who made a study of surgical gloves following operative use. These investigators found that in 74.4 per cent of all operations at least one of the gloves used by the operating team had been torn. Over 22 per cent of all gloves examined had been perforated during operation. Obviously, therefore, simple washing of the gloved hand does not suffice to insure against contamination of the operative field.

Following Antopol's report in 1933, several investigators took the view that talc was responsible for various chronic inflammatory lesions which arose postoperatively, and which resembled lesions associated with foreign bodies. Recently, Eiseman and his associates have made a thorough study of patients suffering from chronic lesions attributed to talcum powder. To rule out any other etiologic agents, these investigators insisted that the pathologic material examined must contain typical talc crystals, around which a foreign body reaction occurred. The granuloma must have occurred at the site of a previous operation, and no other possible source of inflammation could be invoked. Their series contained 37 patients in all of whom these several criteria were fulfilled.

The clinical syndromes were diverse. Most commonly, the patient presented a postoperative wound that had failed to heal (62 per cent). Eighteen patients had chronic sinuses, 5 had fecal fistulas, 7 had intestinal obstructions, and there were various other serious clinical complaints. Tuberculosis was the condition most often confused with talc granuloma. Symptoms had been present for from a few months to twenty-one years. There were 2 deaths in the series of 37 cases.

An adequate substitute for talcum powder has not yet been found. Formaldehyde-treated starch and potassium bitartrate have been used, but these substances have draw-backs. Eiseman and associates suggest, however, that until a better material is found potassium bitartrate, properly sterilized, should be employed.

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This Month in Medicine

ZERO HOUR IN TRAUMA

Speidel of Seattle believes that there is a physical law of repair in the healing of all wounds. Physical, mechanical, chemical, and bacterial changes occur in rapid succession after tissue has been broken or destroyed. Immediate repair aborts many of these changes, and leads to better prognosis and end results. Speidel states the physical law of repair thus: "The healing of a wound is directly proportional to the timeliness of its aseptic coaptation."

Soon after wounding, tissue may be repaired merely by simple, mechanical coaptation. Primary union then occurs, and there is early restoration of function. Within six hours, however, important changes are wrought. The zero hour has passed. healing of the wound becomes more difficult and drawn-out. The earlier the wound is cleansed and the anatomic structures repaired and replaced, the better the chances for quick recovery.

SUGGESTED READING

Speidel, W. C.: The zero hour in the treatment of trauma. Am. J. Surg. 74:576 (November) 1947.

LYMPHOGRANULOMA VENEREUM AND PSITTACOSIS

The disease agent that produces lymphogranuloma venereum is antigenically related to the agents of psittacosis and meningopneumonitis. Until recently, however, this relationship was observable only by complement fixation test. Some months ago Morgan demonstrated that certain of these antigenic relationships could also be observed by skin-sensitivity tests in animals.

Quite recently Pollard and Witka have found that in human beings a skin sensitizing relationship exists between the agents of lymphogranuloma venereum and psittacosis. The antigenic kinship of the two agents was shown by inoculating patients suffering from LGV with antigens prepared from cases of psittacosis. Responses were severe and relatively specific. Although these results are interesting in that they extend our knowledge of the relationships that exist between two entirely separate clinical entities, they do not as yet offer a practical method of differentiating the two diseases.

SUGGESTED READING

Morgan, H. R.: Use of yolk sac antigens for skin tests in rabbits infected with the virus of meningopneumonitis. J. Immunol. 54:1 (September) 1946.

Pollard, M., and Witka, T. M.: The antigenic relationship of lymphogranuloma venereum and psittacosis by skin test in humans. Texas Rpt. on Biol. & Med. 5:288 (Fall) 1947.

STREPTOMYCIN IN TUBERCULOSIS

Taking cognizance of the developing body of opinion regarding the value of streptomycin in pulmonary tuberculosis, the National Health and Medical Research Council of Australia recently has suggested that the antibiotic be employed in certain conditions of tuberculous infection.

Immediate and dramatic effects may be expected in the treatment of generalized hematogenous tuberculosis and tuberculous meningitis with streptomycin. Final results of treatment, however, are not satisfactory.

Caseopneumonic and predominantly exudative forms of tuberculosis respond favorably. The drug is quite effective in controlling an acute spreading lesion following hemoptysis. Improvement usually follows the use of the antibiotic in ulcerative lesions of the larynx, trachea, and bronchus. Preoperative and postoperative use of streptomycin lessens the risk of tuberculous complications and hastens recovery. In genitourinary tract infections the drug produces amelioration of symptoms, but is not cura-

tive. Similarly, in tuberculosis of bones and joints, symptoms regress following use of the drug.

In general, streptomycin produces a bacteriostatic, not a bactericidal effect. Hence, it exerts a suppressive rather than a curative influence upon many forms of human tuberculosis.

SUGGESTED READING

EDITORIAL: Streptomycin in pulmonary tuberculosis. Med. J. Australia 2:558 (November 1) 1947.

ULCERATIVE COLITIS AND HOG STOMACH

EHRLICH, of Boston, has developed a treatment of idiopathic ulcerative colitis, on what appears to be sound rationale.

Recognizing that proteolytic enzymes exist in the colon and rectum, Ehrlich points out that gastrointestinal hypermotility, regardless of the reason for its existence, causes a greater concentration of these enzymes in the colon. Hence the colonic mucosa is predisposed to autolysis.

The investigator now assumes that the intestinal mucosa contains "an anti-proteolytic substance," whose function it is to protect the mucosa from autolysis by the proteolytic enzymes of the intestinal contents. This anti-proteolytic substance is thought to be deficient, at least in a relative sense, in the descending colon and rectum, when a state of gastrointestinal hypermobility exists. Hence, the balance of proteolytic and anti-proteolytic enzymes is upset, and the victim is exposed to varying degrees of mucosal autolysis.

Obviously, if this rationale of ulcerative colitis is correct, any compound that contains an abundance of the anti-proteolytic substance might have sound curative properties. Dessicated extract of hog stomach apparently contains this substance. Ehrlich administered this preparation to 15 patients; the dosage was 3 to 6 heaping tablespoonfuls (30-60 gm.) per day, in divided doses before meals.

In all cases the mucosa was restored, ulceration, inflammation, and spasm disappeared, and the mucosa returned to normal. Four patients with secondary infections were treated with sulfonamides. Four patients relapsed and required a second round of treatment. The hog stomach preparation was administered for a few weeks to three months. Ehrlich regards this treatment as the most specific and promising yet presented for cases of ulcerative colitis of idiopathic origin.

SUGGESTED READING

EHRLICH, R.: Pathogenesis and treatment of ulcerative colitis with extract of hog stomach. Am. J. Digest. Dis. 14:294 (September) 1947.

PENICILLIN BY INTRA-ORAL DRIP

TWO years ago Royston and Deverell described a method of administering penicillin solution by intra-oral drip, over a protracted period of time. Further experiences with the technic in the treatment of cases of Vincent's angina, acute tonsillitis, and other disorders have justified another report, which appeared recently.

The apparatus is simple and easily arranged. It consists of a standard drip-transfusion set; the needle is replaced by a piece of rubber tubing 8 inches long, which is bent to form a J on a piece of dental wire in the lumen. The short limb of the J lies in the buccogingival sulcus; the long limb is attached along the outside of the cheek with adhesive tape. The delivery tube is similarly attached to the nose and forehead, thence to the bottle suspended above the head of the bed. The patient may sleep comfortably without disturbing the tube. The solution is administered at the rate of one pint per twenty-four hours.

Patients seem to like this method of medication. Results are thought to be as good or better than can be obtained with other technics, for the drug is in constant contact with infected areas. The patients had no trouble sleeping while the drug trickled slowly down the pharynx. The tube could even be left in place during meals, or while drinking. Royston believes the method of considerable value in the treatment of faucial infections caused by the Vincent's organism, and in various other severe throat infections, including the first day or two of severe faucial diphtheria.

SUGGESTED READING

ROYSTON, G. R.: Penicillin by intra-oral drip. Brit. M. J. 2:454 (September 20) 1947.

ACNE ROSACEA

Acne rosacea is a cutaneous disease of obscure origin. Writers have attributed its appearance to a wide variety of causes—alcohol, menopause, obesity, exposure to the elements, pies, and so on.

Tulipan recently has reported results of his treatment of 96 patients presenting this disorder. On the basis of his studies of these patients' histories, as well as their presenting symptoms, this author concluded that they were suffering from severe vitamin B deficiency. Hence, he administered large doses of this complex, with a resultant clinical improvement of symptoms.

Tulipan concludes that B-complex deficiency is the primary cause of this disease, that many of the other "causative" agents mentioned in the literature are possibly contributing causes, but not primary.

SUGGESTED READING

Tulipan, L.: Acne rosacea: a vitamin B complex deficiency. Arch. Dermat. & Syph. 56:589 (November) 1947.

PENICILLIN DOSAGE SCHEDULES

Results of an experimental investigation, recently reported by Lubrod, suggest that constant and prolonged concentrations of penicillin in the blood stream are not essential for persistent antibacterial effect. Although results obtained with mice cannot be directly applied to human beings, the therapeutic principles involved are probably similar in both mice and men.

Lubrod has found that the antistreptococcal effect of aqueous penicillin G outlasts the measurable blood levels by many hours. He suggests that a large initial dose has a considerable advantage over schedules in which the total dose is fractionated into many equal parts. This is because in the multiple dose schedules the mice die before enough drug gets into the system to control the infection.

On the basis of these findings, as well as certain confirmatory clinical data in the literature, Lubrod concludes that for penicillin-susceptible infections, infrequent dosage of penicillin is safe and probably as effective as the multiple dose routines. For example, 0.18 gm. (300,000 units) of penicillin G may be administered intramuscularly every twelve hours. Or, if the patient's condition indicates more intensive therapy, an initial dose of 0.6 gm. (1,000,000 units) may be given, followed by the same dose eight to twelve hours later, then reduced doses at twelve-hour intervals.

SUGGESTED READING

Lubrod, C. G.: Comparative efficiency of single and multiple dosage regimens of the penicillins. Bull. Johns Hopkins Hosp. 81:400 (December) 1947.

BAGASSE DISEASE

Bagasse is sugar cane from which the sugar has been extracted. It is pressed into various shapes and used in the manufacture of insulating boards, such as "celotex." Persons working with this material sometimes acquire a respiratory disease, characterized by cough, dyspnea, occasional hemoptysis, night sweats, chills, and low intermittent fever. Miliary mottling occurs in both lungs. Recovery usually follows prolonged illness. The cause of bagasse disease is unknown.

Recently, Gerstl and his associates have attempted to determine the pathogenic properties of bagasse fibers and the microbial content of bagasse suspensions. These investigators inoculated intravenously into rabbits suspensions of unheated bagasse, autoclaved bagasse, and formaldehyde-treated bagasse. The unheated suspensions proved fatal to the animals, except when inoculated in small doses. Numerous necrotizing lesions were found in the kidney and liver, in which fungi were demonstrable; bagasse fibers were not found. When the animals were inoculated with autoclaved or formaldehyde-treated bagasse, no evidence of lesions was observed.

The authors conclude that the bagasse itself did not produce the pathologic conditions characteristic of bagasse disease. Rather the symptoms were thought to have been produced by microorganisms, especially the aspergilli, which were present on or in the bagasse. Bagasse itself is thought to be an inert material.

SUGGESTED READING

Gerstl, B., *et al.*: Pathogenicity of bagasse. Arch. Path. 44:343 (October) 1947.

R. W. C.

Consultation Service

This special consultation information service is offered as a regular monthly feature of *Postgraduate Medicine*. Readers are invited to call on this Service for answers to difficult medical problems from members of our Editorial Board best qualified to help. Each question will be answered by mail and those of general interest will be published each month. Address all communications to Consultation Service, *Postgraduate Medicine*, 512 Essex Building, Minneapolis 2, Minnesota.

FALCIPARUM MALARIA

QUESTION: Will you please advise regarding the management of a case of chronic falciparum malaria. The patient apparently contracted the disease an uncertain length of time ago while working with Navy veterans. Symptoms were precipitated by a change of climate from Maryland to a Southern state during a very hot period.

No chills nor fever occurred but the disease was manifested by malaise, anorexia, and extreme fatigability, especially in late afternoon with a slight rise in temperature. Thin blood smears revealed a high infestation percentage with trophozoites and gametocytes. There is no splenomegaly nor evidences of cerebral damage. There is no history of an acute malarial episode. The patient has never left the limits of continental U. S. and has never employed suppressive medication.

Since the infection was discovered in June, he has been given three therapeutic courses of atabrine with little change in either symptoms or the blood smear picture. A course of plasmochin is contemplated when clinical improvement occurs. What are the possibilities of precipitating a "black-water" fever episode by further intensive therapy?

M.D.—Indiana

ANSWER: There does not appear to be any possibility of precipitating a "black-water" fever episode by further treatment of this patient. The history of this patient is a very unusual one for infection with Plasmodium falciparum. This type of malaria is the one which is most readily controlled by therapeutic courses of atabrine and also the one which gives the fewest number of relapses.

The statement that thin blood smear revealed a high percentage of infection with trophozoites and gametocytes and that there was no change in this condition following treatment is not consistent with what is generally understood to be true in cases of this type. For this reason it is suggested that a properly prepared slide be submitted to an experienced malariologist to determine if this is actually an instance of infection with Plasmodium falciparum.

To the Editor:

In your issue of Postgraduate Medicine, Volume 2, Number 5, November 1947, in answer to an inquiry regarding "Treatment of Lues" you make the following statement:

"It might well be that the relapse of results of serologic tests of the blood are due to the fact that the patient's cerebrospinal fluid is positive."

How much penicillin did this patient receive? This certainly is one factor the doctor asking the question should have asked, because the greater the concentration used, the greater the penicillin blood level would be, making quite an enormous difference to compare a daily wax injection of 300,000 penicillin with one of 1,000,000.

"However, this afforded no demonstrable relief." In what way was there no relief? As the author of this question continues, he mentions that after mapharsen and bismuth subsalicylate, the patient had a negative Kolmer and a strongly positive Mazzini, suggesting that he judges cures by these reactions alone.

In answer to the above problem of penicillin therapy in the light of persisting high serologic titers, the following statement (published in the Journal of the American Medical Association, Volume 134, Number 18, August 30, 1947: special article on "The Management of Syphilis" by the Veterans Administration, Washington, D. C.) makes the answer to our problem simple: "The rise in titer or the change from negative to positive that often occurs during or soon after completion of penicillin treatment will not be construed as evidence of serologic relapse."

Very truly yours,

Gabriel F. Greco, M.D. Ozone Park, N. Y.

New Drugs

Information published in this department has been supplied by the manufacturers of the products described

PNEUMOCOCCUS POLYSACCHARIDES (TYPE-SPECIFIC) SQUIBB

PURPOSE: To aid in reducing the incidence and carrier rate of pneumonia resulting from the types of pneumococci represented in the antigenic mixture; also in controlling epidemics of these types.

DESCRIPTION: An antigenic solution of the capsular polysaccharides of the most common types of pneumococci. Supplied in two combinations of the types of pneumococci to which adults and children, respectively, are believed to be most susceptible. Each combination contains per cc. at least 0.06 mg. of each of the component polysaccharides, made up in sterile aqueous isotonic solution of sodium chloride containing 0.5 per cent phenol.

INDICATIONS FOR USE: Immunization for older persons and for the very young; also, where possible, for those undergoing surgery or recovering from severe illness; for persons subject to repeated attacks of pneumonia, or unable to tolerate sulfa drugs or other known remedies for pneumonia; in institutions where pneumonia frequently occurs in epidemic form; and for special occupational groups, in whom the incidence of and mortality from pneumonia is unusually high.

ADMINISTRATION AND DOSAGE: For adults and children over 12 years of age, a single 1 cc. injection subcutaneously; for children under that age, 0.5 cc. Immunity usually develops within two weeks and is effective for at least one year. Reactions generally are mild and consist chiefly of slight soreness of the arm lasting for a few days only.

HOW SUPPLIED: Combinations A (primarily for adults) and B (for children) of Solution Pneumococcus Polysaccharides in 1 cc. rubber-stoppered vials, in boxes of 5; and in 5 cc. rubber-stoppered vials, in boxes of 10. Potency period is one year.

PRODUCER: E. R. Squibb & Sons, New York, N. Y.

PYRIBENZAMINE OINTMENT AND CREAM

PURPOSE: Topically applied Pyribenzamine exercises a local antihistaminic action thereby alleviating pruritus and allergic skin manifestations.

COMPOSITION: Pyribenzamine ointment and cream contain a 2 per cent concentration of the active antihistaminic agent. Prepared respectively in a petrolatum base and a water-washable vehicle.

INDICATIONS FOR USE: In the treatment of atopic dermatitis, pruritus ani, contact dermatitis, neuro dermatitis, lichen planus, and lichen chronicus simplex. Also for the general alleviation of pruritus in nonspecific skin disorders.

DOSAGE AND ADMINISTRATION: Topical application. A light dressing should usually be applied following application of the ointment.

CAUTIONS: Significant systemic absorption may occur if ointment or cream are applied to extensive raw areas. In rare instances a contact type of eczematous allergic reaction may occur.

HOW SUPPLIED: Pyribenzamine ointment and cream in jars of 50 gm. and one pound.

PRODUCER: Ciba Pharmaceutical Products, Inc., Summit, N. J.

INFAZYME

PURPOSE: Nutrient tonic including the essential amino acids designed especially for the "sickly" child. Supplies the essential and supplementary factors of the vitamin B complex; hematinic tonic; dietary supplement; aids in increasing appetite, and in intestinal absorption and assimilation.

COMPOSITION: Contents per 15 cc. (approximately three teaspoonfuls):

Protein hydrolysate (45% amino acids)	5.0 gm.
Thiamine hydrochloride (Vitamin B_1)	3.0 mg.
Riboflavin (Vitamin B_2)	2.0 mg.
Niacinamide	12.0 mg.
Pyridoxine hydrochloride (Vitamin B_6)	1.0 mg.
Peptonized iron (N.F.)	135.0 mg.
Liver, B-Complex Fraction	67.5 mg.
Rice Bran Extract	67.5 mg.

(Formula expressed in terms of recommended dosage for children 6 to 12 years of age.)

DESCRIPTION: Features a rich fruity taste that particularly appeals to children.

DOSAGE AND ADMINISTRATION: Children 6 to 12 years of age, 5 cc. (one teaspoonful) three times daily. Children 1 to 6 years of age, 5 cc. twice daily. Infants, 5 cc. daily. May be mixed with milk, water, or juices and taken either before or during meals. For infants, may be mixed with feedings.

HOW SUPPLIED: 4 oz. and 12 oz. bottles.

PRODUCER: The Wm. S. Merrell Company, Cincinnati, Ohio.

HEMO-PAK

PURPOSE: Hemostatic absorbable gauze and cotton dressings.

DESCRIPTION: Prepared from oxidized cellulose, it effects hemostasis within two minutes after application to the bleeding points. When exposed to blood, Hemo-Pak oxidized gauze or cotton turns black and forms a soft gelatinous mass which readily molds itself to irregular surface contours and controls hemorrhage.

INDICATIONS FOR USE: Hemo-Pak gauze packing strips, 14 inches by 2 inches, are useful in general and urologic surgery for control of venous or capillary hemorrhage or small arterial hemorrhage when suturing or ligation is impractical. Hemo-Pak gauze packing strips, ½ inch by 2½ yards, are especially adapted to otolaryngological procedures. Hemo-Pak cotton pads, 6 inches by 2 inches, are useful in neurologic surgery and ear, nose, and throat procedures.

PRODUCER: Johnson & Johnson, New Brunswick, N. J.

RAYOPAKE

PURPOSE: A new, water-soluble contrast medium for x-ray studies of the uterus, fallopian tubes, bladder, and urethra.

COMPOSITION: A viscous, aqueous solution, containing 50 per cent diethanolamine salt of 2,4-dioxo-3-iodo-6 methyl tetrahydropyridine-N-acetic acid and 4.8 per cent polyvinyl alcohol, with 0.1 per cent benzalkonium chloride as preservative.

DESCRIPTION: Readily miscible with urine, making aspiration following its use unnecessary. The high viscosity of Rayopake is of particular advantage in outlining the lumen of the uterus, tubes, bladder, and urethra but it prevents its use in other body cavities.

HOW SUPPLIED: Available in 7.5 cc. vials for hysterosalpingography and 35 cc. vials for cystourethrography.

PRODUCER: Hoffman-La Roche Inc., Nutley, N. J.

CREMOMERAZINE AND CREMODIAZINE

PURPOSE: For use in the treatment of pneumonia, meningitis, and other diseases susceptible to treatment by sulfonamides.

COMPOSITION: A new dosage form for sulfamerazine and sulfadiazine.

DESCRIPTION: A palatable, pleasant flavored suspension widely acceptable to the child or adult patient.

INDICATIONS FOR USE: In the treatment of diseases susceptible to sulfonamides.

HOW SUPPLIED: In 16 fluid ounce "Spasaver" bottles.

PRODUCER: Sharp & Dohme, Inc., Philadelphia, Pa.

NITRAMAC TABLETS

PURPOSE: To supply amino acids of a high biologic potency in tablet form, providing a tasteless method of administering oral amino acids.

COMPOSITION: Each tablet contains 0.4 gm. protein. The composition of the protein hydrolysate from which Nitramac Tablets are made is as follows:

Protein	75%
Carbohydrate	14%
Fat	0.3%
Ash	6%

DESCRIPTION: Designed to supplement the dietary intake of protein with protein in predigested amino acid form.

INDICATIONS FOR USE: As a supplement where amino acid therapy is desired in peptic ulcer, pregnancy and lactation, hyperpyrexia, preoperative and postoperative states, digestive deficiencies, extensive burns, diarrhea, and hemorrhage.

DOSAGE: Varied according to needs of the patient. Five tablets four times daily supply 8 gm. of predigested protein.

HOW SUPPLIED: In bottles of 100, 250, and 1,000 tablets.

PRODUCER: The Maltine Company, New York, N. Y.

Medicine Makes News

COMMITTEE ORGANIZED TO ESTABLISH RESEARCH FOUNDATION

In the first such joint action by the pharmaceutical industry and medical profession, a committee to be known as THE PHARMACEUTICAL-MEDICAL RESEARCH FOUNDATION has been organized to establish a new foundation for basic medical research, to improve the public health. It includes representatives from the pharmaceutical (including the medicinal chemical) industry and the medical profession. The committee will be financially supported, in major part, by the pharmaceutical industry as a contribution to the national welfare.

Representatives from the pharmaceutical industry are: S. DeWitt Clough, chairman of the board, Abbott Laboratories; A. H. Fiske, vice president, Eli Lilly and Company; Elmer H. Bobst, president, William R. Warner & Co., Inc.; John L. Smith, president, Chas. Pfizer & Co., Inc.; S. Barksdale Penick, Jr., president, S. B. Penick & Co.; M. C. Eaton, president, Norwich Pharmacal Co., and Charles Wesley Dunn, of the New York Bar. The representatives from the medical profession are the following officers of the American Medical Association: Dr. R. L. Sensenich, president-elect; Dr. E. L. Henderson, chairman of the Board of Trustees; Dr. Ernest E. Irons, secretary of the Board of Trustees; Dr. Morris Fishbein, editor of the *Journal,* and Dr. Austin Smith, secretary of the Council on Pharmacy and Chemistry. Dr. Sensenich is chairman of the committee.

The foundation will be a wholly public institution in purpose, conduct, and service, including on its governing board distinguished and appropriate representatives of the general public, in addition to leading representatives of the pharmaceutical industry and medical profession. The board will determine its program of scientific research on the basis of a recommendation by an authoritative scientific advisory committee and the advice of an eminent scientific director. It is contemplated that the initial basic research by the foundation will be in the field of degenerative diseases.

EPILEPSY NOW A REPORTABLE DISEASE

Epilepsy has been made a reportable disease by action of the Wisconsin State Legislature, in the interest of promoting safety on highways. According to a notice released by the State Board of Health, the Act requires every physician to "report name, age, and address of every person diagnosed as afflicted with epilepsy or similar disorder characterized by lapses of consciousness." It further requires local boards of health or city health commissioners to report to the State Board of Health in writing the name, age, and address of every person reported to them as epileptic, and the State Board of Health in turn is required to make the same report to the motor vehicle department.

In compliance with this same statute, the State Board of Health has promulgated the following definition of epilepsy:

"An affection of the nervous system characterized by attacks of unconsciousness, with or without convulsions, shall be considered as epilepsy in carrying out the provisions of section 146.23, 140.05 (13), and 141.08 of the Wisconsin Statutes."

Correspondence Dept.

To the Editor:

I have read with interest the article by Dr. Nils Larsen in the November 1947 issue of this journal. His report is of value and contains a rather interesting contribution on the problem of fluorine-containing tablets in the control of dental caries. However, there are a few facts that are obscured by an apparent lack of familiarity with some of the recent work in the dental caries field.

The material discussed in the first part of the paper on nutrition and diet in regard to dental caries has been more or less discarded. Dr. Larsen points out that some candy eaters have no decay whereas many low sugar eaters have considerable decay and suggests that this may be an argument against carbohydrate as a factor in dental caries. We now recognize that there are various degrees of immunity to dental caries and that an individual who is immune to dental caries may eat large quantities of refined carbohydrate without developing caries, whereas the highly susceptible individual may eat only a small amount of carbohydrates and produce much acid in dental plaques. Certain immune individuals may produce the acid in the plaques at such a rate that it does not attack the enamel. This situation is quite comparable to an individual's being immune to a general systemic disease such as tuberculosis, diphtheria, or any of the other communicable diseases, although a different mechanism appears to be involved in the local bacterial enzyme system. The fact that Dr. Howe fed sugar balls to monkeys for eight months and they did not develop dental caries simply re-emphasizes a well known fact that monkeys are relatively immune to dental caries.

On page 363, Dr. Larsen stated, "because of inconclusive evidence, some of the dentists are now using a 2 per cent sodium fluoride solution to paint the teeth three times a year after a thorough cleansing." The inconclusive evidence that Dr. Larsen mentioned has been replaced by the results of very careful studies in Minnesota, Ohio, and other places by the United States Public Health Service and independent investigators who have now established that the application of a 2 per cent sodium fluoride solution to the teeth of children, four times within a short period after prophylaxis, reduces dental caries by 40 per cent in population groups. The statement about inconclusive evidence should be discarded because of recent studies.

The fact that fluorine-containing tablets did not control dental caries is a very important finding. The blind test which Dr. Larsen used could well be adopted by other investigators of this problem. It is very difficult to evaluate the results of caries control because of the slow process of the disease. It is sometimes a matter of many months or years before carious lesions become observable. The method that he used bears out this observation. It is more important that the lactobacillus counts did not show any reduction on the fluoride-containing tablets. The lactobacillus counts, while not infallible, are valuable indicators of the activity of dental caries and have a place in all well controlled caries studies. Certainly, Dr. Larsen's study is more complete and better controlled than that used to recommend fluoride-containing tablets.

The present status of fluoride-caries investigations justifies the following statements:

1. Fluorine, occurring naturally, in communal water in concentrations of about 1 p.p.m. results in lower caries experience than in nonfluoride water areas in children born and raised on the waters.

2. Experiments on the effect of artificially fluorinating waters, such as are in progress at Kingston-Newburgh, Evanston, Illinois, Grand Rapids, and other cities, are justified and when the results are available the advisability of general fluorinization can be determined.

3. The application of 2 per cent solution of sodium fluoride to the teeth of children in four treatments after prophylaxis results in a caries reduction of about 40 per cent in population groups. Such treatment has adequate evidence to justify general use.

4. Evidence available today does not justify the use of any fluorine-containing compound for home use or self-administration.

Sincerely yours,

Hamilton B. G. Robinson, D.D.S., *Dean,*
College of Dentistry, Ohio State University.

AFTER HOURS

By FRANK G. SLAUGHTER, M. D.

It is our painful duty to report that the profession of medicine in its present form is all shot to pieces, flat on its back . . . in short, KAPUT. And all because in our zeal to be scientific and make everybody live to a hundred, we have devised a set of instruments of precision which have now turned upon us, Frankenstein-like, to destroy us.

A man in Jacksonville, Florida, named Rowland, has invented a devilishly ingenious little machine which he calls a PHOTOMICRON. Put a specimen of blood under this innocent little apparatus and it tells you the white and red blood counts and the hemoglobin, in less time than it takes to focus an ordinary microscope. *All with the turn of a switch.* Furthermore, this thing really works. We had a demonstration of it the other day and afterwards staggered, pale and shaking, out of the building and across the street to the nearest barroom for a couple of quick ones to help regain our equilibrium.

It is only a matter of time now until curvaceous blond laboratory technicians will be replaced by massive black and repulsive machines that do everything from blood sugars to urethral smears and print the result on a ticker tape. *The horror of it all!* No more to drop into the laboratory at the end of a long day and get that predinner lift from the sight of white sharkskin stretched snugly over the entrancing curve of the gluteus, or to relax with a cigarette between hormone injections, and enjoy the unparalleled revelations of a starched uniform hemline. The world will truly be a sadder place without these things.

But all is not lost. We saw this catastrophe coming many years ago and we've had a group of scientists working in our secret laboratory, getting ready for the new world of the machine in medicine. If it's machines they want, we've got them, *dozens of them,* all ready to go at the drop of a dollar . . . in the slot, of course.

We've been holding back our discoveries because we knew the effect they would have on medical practice and we hesitated to unleash the demon of the machine. But now that the secret is out, we're going ahead full steam with our campaign to save the profession from destruction.

Our first invention, the U-REEN-A, is such a simple gadget that we hesitated even to mention it. Attached to the laboratory sink, it shoots a beam of light through a tube of urine, says, "Hmm," and dumps the specimen in the sink, stamping *Negative* on the report slip at the same time. Our SUPER-U-REEN-A, however, is something else and well worth the additional cost. (We feel like a dog for introducing commerce into a high planed scientific discussion like this, but after all we have to eat.) It heats the specimen, determines the albumin by a photoelectric cell, tests for sugar and specific gravity, and examines it with the automatic microscope, all in one operation, completed while you light a cigarette.

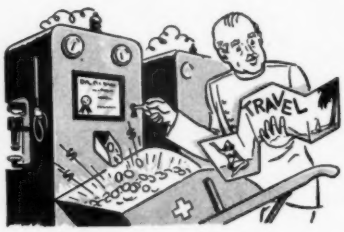
One of our more elaborate instruments, the TONSILLOTRON, or PHARYNGOTRON, is especially designed to be placed in restaurants. When the patron opens his mouth for the first bite, the instrument shoots a beam of light into the pharynx, measures both diameters of the tonsils, and the elevation above the floor of the fossa in a fraction of a second. Then the mechanical brain instantly calculates the volume of the tonsils and when it reaches a critical level, the instrument says sharply, *"Those tonsils look terrible; they'll have to come out right away."*

While the patient is gagging over his soup, the instrument hands him an appointment with the surgeon owning the instrument and makes a reservation at the nearest hospital. For a slight extra charge, another model will also collect both hospital insurance and professional fee in advance.

We expect to license our SUPER-LARYNGOTRON only to certified nose and throat specialists. This model examines the patient who has already had the tonsils removed and murmurs, *"Those tags look pretty bad. Don't you have a lot of trouble with rheumatism, indigestion, insomnia, vague pains, getting up at night,*

belching, gas on the stomach, constipation, impotence, or frigidity?" When the patient answers *"Yes,"* (as who wouldn't) the machine also makes arrangements for the operation and collects fees and hospital insurance in advance.

Because of the high incidence of neurosis and psychosomatic disorders, we have recently invented the HYPNOTRON. An accusing eye stares at the patient while a soft voice intones, *"Sleepy. Sleepy. Sleepy."* When the head drops and touches a switch, the machine says, *"Now tell me everything."* As the patient spills the life story, a wire recorder makes a record of it and flashes it by teletype to the editors of "Intimate Romances." At the end the patient is given post-hypnotic suggestions and goosed into wakefulness with an electric shock. An advanced model called the PSYCHOSOMATRON gives electric shock therapy and psychotherapy at the same sitting.



OUR crowning achievement, of course, is the GONOTRON, and our motto is, *"A Gonotron in every man's room."* This handy little gadget is going to revolutionize venereal disease control. The GONOTRON takes a urethral smear, stains it, and scans it with a cathode ray. When it comes to a pus cell, a smaller ray takes over and scans the cell. A biscuit-shaped diplococcus hasn't a chance with such an instrument as this. But most important, the GONOTRON doesn't stop at diagnosis; it treats as well. Once it has spotted a gonococcus, it injects 300,000 units of penicillin (Romansky formula, of course) and gives a short recorded sex hygiene lecture.

Modestly, we hesitate to mention such simple devices as our mechanical finger for rectal examinations, or the double model, the GYNOTRON for the gynecologist. We are rather proud, however, of the CORONOTRON. It takes an electrocardiogram, develops it, scans it with the photoelectric eye, and when it reaches a depressed S-T segment, phones the nearest hospital for an ambulance and flashes a *Stand-By* signal to the local undertaker.

We are confident that our machines are going to make a new world for the doctor, the first break he's had since Hippocrates. With a battery of these mechanical goldmines placed strategically around town, he can sit back and listen to the tinkle of dollars dropping into slots and know that medicine is marching on to new scientific heights and new horizons. In the *Full Life*, doctors will make rounds once or twice daily to empty the tills of these mechanical medicos and stagger to the bank with a load of coin. No more night calls, no more talking to relatives. *What a happy prospect!* Winter at Palm Beach; summer in the Canadian Alps!

And what a change this is going to make in medical education. No more hours spent poring over microscopes, pulling blood smears, or boiling urine. The medical student of tomorrow will work a six hour day, or less, with plenty of time for the real pleasures of the medical course. Then the study of medicine will be what it once was, an occupation for a gentleman.

Well, that's the story. We're off now to collect the take from our experimental battery of machines that we've installed in the local penny arcade, and then off to the races . . .

Damn that telephone! . . . *Hello . . . A patient? . . . Female? . . . Give her the Gynotron . . . What? . . . A case of nymphomania . . . Hold everything! We'll treat this case in person!*

INTERNATIONAL ASSEMBLY

PUBLIC AUDITORIUM, CLEVELAND, OHIO

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